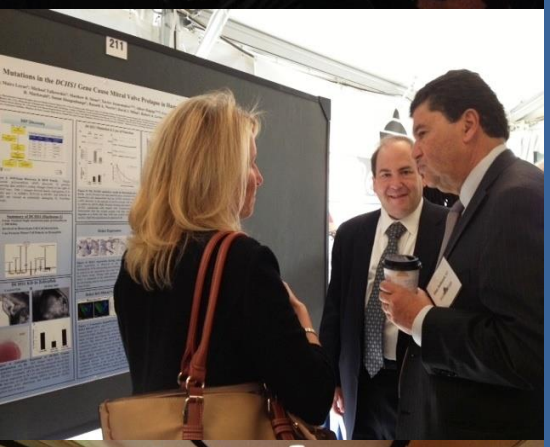
MGH Clinical Research Day



15th Annual Celebration of Clinical Research

October 5, 2017
8 am – 1 pm

O'Keeffe Auditorium &
Bulfinch Tents

Welcome to Clinical Research Day 2017

Clinical Research Day is an annual celebration of clinical and translational investigators and their accomplishments over the past twelve months at the Massachusetts General Hospital (MGH). Every year the clinical research community at MGH becomes more vibrant and robust with this year being no exception. This year, we had an unprecedented **340** abstract submissions reflecting the exciting work being conducted by clinical research teams here at MGH. Clinical Research Day is a great opportunity for interaction between clinical researchers and for learning more about the different types of research being conducted at our Institution. It is also an opportunity for sharing ideas that may contribute to strategic thinking and future planning.

Our Keynote Speaker is **Daniel Rader, M.D.,** Seymour Gray Professor of Molecular Medicine, Chair, Department of Genetics, Perelman School of Medicine at the University of Pennsylvania and Children's Hospital of Philadelphia. Dr. Rader will give a talk entitled "**Genomic and Precision Medicine: Its time has arrived**".

Following the Keynote Address by Dr. Rader, there will be two poster sessions and a panel discussion:

9 to 11 am Poster Session I: **Individual Submissions**
Bulfinch Tents

11 to noon Panel Discussion
O'Keeffe Auditorium **How is Personalized Medicine Impacting Care Now and Shaping Our Future?**

Moderator:
Maurizio Fava, M.D., Director, Division of Clinical Research,
MGH Research Institute
Panel Members:
Daniel Rader, M.D., Chair, Department of Genetics, Perelman School of Medicine
University of Pennsylvania and Children's Hospital of Philadelphia
Roy Perlis, M.D., Director, Center for Quantitative Health and
Director, Center for Experimental Drugs and Diagnostics, Psychiatry, MGH
James Meigs, M.D., M.P.H., Division of General Internal Medicine, MGH
Alice Shaw, M.D., Ph.D., Thoracic Cancer Program, MGH
Christine Seidman, M.D., Director, Cardiovascular Genetics Center, BWH

Noon to 1 pm Poster Session II: **Team Submissions**
Bulfinch Tents

Maurizio Fava, M.D.
Director, Division of Clinical Research, MGH Research Institute

Acknowledgements

Clinical Research Day is a collaborative effort amongst the clinical research community. We wish to acknowledge investigators who submitted abstracts, mentors who encouraged them and departmental leaders who continuously nurture clinical investigation at MGH. They deserve our collective gratitude for doing this important work.

We would also like to thank the chiefs for their sponsorship of departmental awards:

- Jeanine P. Wiener-Kronish, M.D., Anesthesia
- David E. Fisher, M.D., Ph.D., Dermatology
- David F.M. Brown, M.D., Emergency Medicine
- Katrina A. Armstrong, M.D., Medicine
- Merit E. Cudkowicz, M.D., Neurology
- Jeffrey L. Ecker, M.D., Ob/Gyn
- Andrew A. Freiberg, M.D., Orthopaedic Surgery
- David N. Louis, M.D., Pathology
- Allan J. Goldstein, M.D., Pediatric Surgery
- Ronald E. Kleinman, M.D., Pediatrics
- Timothy G. Ferris, M.D., MGPO
- Jerrold F. Rosenbaum, M.D., Psychiatry
- James A. Brink, M.D., Radiology
- Keith D. Lillemoe, M.D., Surgery

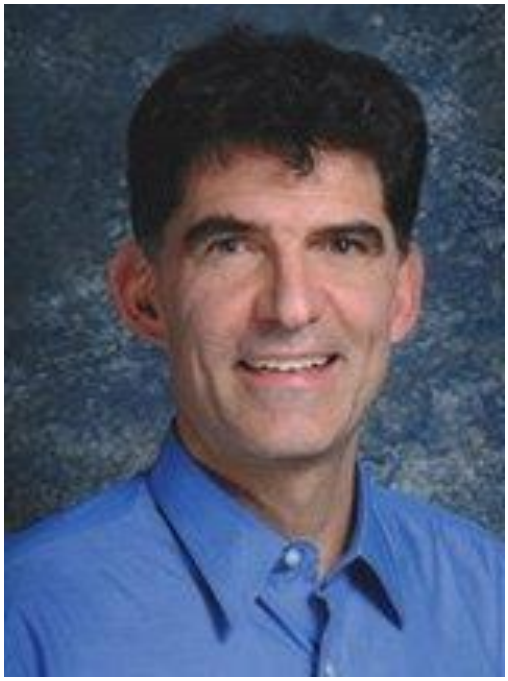
Faculty and staff of the MGH Division of Clinical Research contributed valuable ideas, time and energy to make this day possible. We thank you all for your help and support.

Special thanks are due to:

- Andrew Nierenberg, M.D., and Karen Miller, M.D., Co-Directors, Training and Education, MGH Research Institute
- Kelsey Gay, Stacey Grabert, Tatiana Koretskaia and Cassidy Peters

A very special thank you to **Tiereny Morrison-Rohlfs** for her leadership and hard work to make Clinical Research Day a success.

Keynote Speaker



Daniel J. Rader, MD is the Seymour Gray Professor of Molecular Medicine at UPenn, Chair of the Department of Genetics in the Perelman School of Medicine at the UPenn, and Chief of the Division of Translational Medicine and Human Genetics, Department of Medicine at UPenn.

Dr. Rader is one of the world leaders in precision medicine; he has had a long interest in Mendelian disorders of lipoprotein metabolism and in the development of novel therapies for these disorders.

Hospital-Wide Awards

Poster #

$2,500 Team Awards (2)

IMMERSE: Improving medication renewal management to reduce burden and improve care

64

Crocker, J. Benjamin; *Hoover, Melissa; Nixon, Victoria; Lang, Brian J; Lynch, Stephen H.; Goodridge, Nicole*

Massachusetts General Physicians Organization (MGPO)

Deep Learning for Rapid, Accurate, Automated Detection & Characterization of Intracranial Hemorrhage on Unenhanced Head CT

193

Mansouri, Mohammad; *Lee, Hyunkwang; Cho, Jung Hwan; Pomerantz, Stuart; Romero, Javier; Almeida, Renata Rocha De; Kamalian, Shahmir; Gonzalez, Ramon Gilberto; Lev, Michael; Do, Synho*

Radiology

$750 Translational Research Award (2) sponsored by Molecular Biology

The Gut Microbiome and Susceptibility to Vibrio cholerae Infection

318

Weil, Ana; *Midani, Firas; Chowdhury, Fahima; Khan, Ashraful; Ellis, Crystal; Durand, Heather; Reese, Aspen; Silverman, Justin; Nimmagadda, Sai; Ryan, Edward; Calderwood, Stephen; Harris, Jason; Qadri, Firdausi; David, Lawrence; LaRocque, Regina*

Medicine - Infectious Diseases

Evidence from Human Genetics and Zebrafish Modeling For Heterozygous Loss of Function Mutations in TCF12, a Basic Helix-Loop Helix Transcription Factor, as a Cause of Kallmann Syndrome and a Critical Role in GnRH Neuronal Ontogeny

149

Keefe, David Lawrence; *Balasubramanian, Ravikumar; Davis, Erica; Katsanis, Nicholas; Crowley, William J*

Medicine - Endocrine-Reproductive Endocrine

$500 Individual Award (2)

Does the Mixed Opiod Recepter Antagonist Naltrexone Mitigate Stimulant-Induced Euphoria?: A DoubleBlind, Placebo Controlled Trial of Naltrexone

248

Spencer, Thomas J; Bhide, Pradeep; ***Pulli, Alexa;*** *Fitzgerald, Maura; Yule, Amy; Uchida, Mai; Storch, Barbara; Biederman, Joseph*

Psychiatry

Adjuvant versus early salvage post-prostatectomy radiotherapy for prostate cancer with adverse pathologic features: a multi-institutional analysis

135

Hwang, William L; *Tendulkar, Rahul D; Niemierko, Andrzej; Agrawal, Shree; Stephans, Kevin L; Spratt, Daniel E; Hearn, Jason W; Koontz, Bridget F; Lee, W. Robert; Michalski, Jeff M; Pisansky, Thomas M; Liauw, Stanley L; Abramowitz, Matthew C; Pollack, Alan; Moghanaki, Drew; Anscher, Mitchell S; Den, Robert B; Zietman, Anthony L; Stephenson, Andrew J; Efstathiou, Jason A*

Radiation Oncology

		Poster number
Anesthesia		
Race and Sex Both Affect Pain Management in the Emergency Department **Julia Rosenbloom**	$1,000	*262*
Titration of positive end expiratory pressure restores homogeneous ventilation in mechanically ventilated hypoxic obese patients **Roberta Santiago**	$500	*269*
Conventional thermal versus water-cooled genicular nerve radiofrequency lesioning (RFL): a retrospective chart review. **Cristina Shea**	$250	*285*
Spread of injectate solution during T4 Retrolaminar Block (RB); a study on eight fresh frozen cadaveric models **Sassan Sabouri**	$500	*267*
Association of nutritional deficit with functional status at the time of discharge from the intensive care unit in critically ill surgical patients **Shu Lu**	$250	*264*
Self-reported sleep traits share common genetic architecture with psychiatric disorders and migraine **Jacqueline Lane**	$250	*159*
Dermatology		
Combined treatment of X-rays with UVC emitting nanoparticles results in a synergistic decrease in cell viability **Matthias Mueller**	$500	*215*
Emergency Medicine		
The Utility of Repeat Routine Computerized Tomography Scans in Patients With Mild Traumatic Intracranial Hemorrhage **Jonathan Van Ornam**	$750	*304*
ED-to-ICU Return Admissions: A Better Surrogate Measure for Quality Assurance in the Emergency Department **Kelley Wittbold**	$500	*325*
Medicine		
Impact of a Population Health Management Intervention on Racial Health Disparities in Cardiovascular Disease **Aisha James**	$1,000	*141*
Human and Microbial Genetic Factors Important in Tick-Borne Disease **Jacob Lemieux**	$500	*167*
Neurology		
Investigation of the Neural Dynamics of Human Motor Learning Using an Intracortical Brain Computer Interface **David Lin**	$500	*177*
Unbiased pathogen detection in patients with central nervous system infection using metagenomic sequencing **Shibani Mukerji**	$500	*242*

Ob/Gyn

ARE TIME-LAPSE (TL) MORPHOKINETIC PARAMETERS USEFUL IN PREDICTING PREGNANCY ESTABLISHMENT AND VIABILITY? A RETROSPECTIVE COHORT STUDY OF 223 WOMEN UNDERGOING IN VITRO FERTILIZATION WITH SINGLE EMBRYO TRANSFER (IVF/SET)
Georgios Christou $500 *56*

THE EFFECTS OF CLOMIPHENE CITRATE (CC) INITIATION DAY AND DOSE ON EARLY PREGNANCY OUTCOMES?
Eduardo Hariton $500 *120*

Orthopaedic Surgery

Initial Opioid Dosing Influences Long-Term Use: An Instrumental Variables Approach
Matthew Basilico $1,000 *22*

Pathology

White Blood Cell Population Dynamics for Risk Stratification Of Acute Coronary Syndrome
Anwesha Chaudhury $500 *51*

Pediatric Surgery

Concurrent MIS treatment during chemotherapy preserves the ovarian reserve and fertility
Motohiro Kano $500 *148*

Pediatrics

ZONULIN TRANSGENIC MOUSE AS A MODEL OF GUT-BRAIN AXIS CROSSTALK INFLUENCING BEHAVIOR
Brett Nelson $500 *208*

Performance Analysis & Improvement/Practice Improvement

The impact of workplace engagement on physicians with high and low levels of burnout
Sara Lehrhoff $1,000 *166*

Psychiatry

Associations between Amygdala Connectivity, Psychopathology, and Implicit Negativity Bias
Benjamin Shapero $200 *283*

The neural basis of generalization of fear and safety signals and alterations in these processes in subthreshold psychosis
Logan Leathem $200 *161*

Memory Deficits are Reversible with Sustained Cannabis Abstinence among Cannabis Using Adolescents
Randi Schuster $200 *274*

Does the Mixed Opioid Recepter Antagonist Naltrexone Mitigate Stimulant-Induced Euphoria?: A DoubleBlind, Placebo Controlled Trial of Naltrexone
Alexa Pulli $100 *248*

Functional Connectivity with Transcranial Magnetic Stimulation Reveals Default Mode Network Mechanisms of Depression
Erik Lee $100 *164*

Enhanced connectivity between caudate and default mode networks in anorexia nervosa is associated with increased drive for thinness and trait anxiety
Kendra Becker $100 *26*

Radiology

Brain Circuit-Gene Expression Relationships and Neuroplasticity of Multisensory Cortices in Blind Children.
Laura Ortiz-Terán $500 *231*

Point-of-Care Virtual Radiology Consultations in Primary Care: a New Model for Patient-Centered Care in Radiology
Dania Daye`` $500 *72*

Surgery

Concurrent MIS treatment during chemotherapy preserves the ovarian reserve and fertility
Motohiro Kano $250 *148*

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1

Mohamed E. Abdelaziz, MD, Orthopedics

Arthroscopic Characterization of Purely Ligamentous Syndesmotic Instability: Exactly What Measurement Matters?

M.E. Abdelaziz[1,2], J. Massri-Pugin[1], B. Lubberts[1], B. Vopat[1], D. Guss[1], A.H. Johnson[1] and C. DiGiovanni[1]
[1]Orthopedics, MGH, Weymouth, MA, USA and [2]Mansoura Medical School, Mansoura, Egypt

Introduction: Ankle arthroscopy is increasingly used to diagnose syndesmostic instability by visualizing the distal tibiofibular articulation and applying a lateral fibular stress. Precisely where in the incisura one should measure potential diastasis, however, remains unclear. The purpose of this study was to determine where within the incisura one should assess coronal plane instability in purely ligamentous syndesmotic injuries when performing a lateral hook stress test (LHT).
Methods: Twenty-two above-knee cadaveric specimens underwent ankle arthroscopy, first with intact ligaments and thereafter after each sequential step of syndesmotic and deltoid ligament transection (Figure 1). At each step, a standard 100N hook test was applied through a lateral incision 5 cm proximal to the ankle joint and the coronal plane diastasis in the stressed and unstressed states were measured at both anterior and posterior third of the distal tibiofibular joint using calibrated probes ranged from 0.1 to 6.0 mm, with 0.1 mm of increments.
Results: Anterior third diastasis did not change significantly when applying a LHT, neither in the intact state nor after any stage of ligament transection (*P* values ranging from p=0.61 to p=0.94). In contrast, posterior third diastasis increased significantly by applying stress at the intact state at the following stages of transection: posterior-inferior tibiofibular ligament (PITFL), PITFL plus interosseous ligament, all syndesmosis ligaments, and all syndesmosis ligaments plus superficial and deep deltoid ligament (*P* values ranging p=0.001 to p=0.031). Interobserver agreement was substantial (ICC = 0.81; 95% confidence interval, 0.44-0.92), and moderate (ICC = 0.73; 95% confidence interval, 0.36-0.87) for anterior and posterior third diastasis measurements, respectively.
Conclusion: Syndesmotic ligament injury results in coronal plane instability of the distal tibiofibular articulation that is readily identified arthroscopically with a LHT and when measured in the posterior third of the incisura. Measurement at the anterior third of the incisura may miss such injuries.

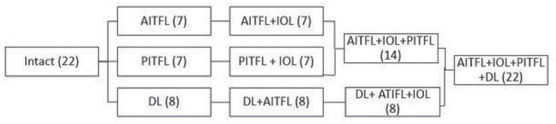

Figure 1. Different sequential sectioning used in each group.
Abbreviations: AITFL, anterior-inferior tibiofibular ligament; IOL, interosseous ligament; PITFL, posterior-inferior tibiofibular ligament; DL, deltoid ligament.

Table 1. Anterior and Posterior diastasis with and without the lateral hook test during each stage of transection

Stage of transection	Anterior third diastasis			Posterior third diastasis		
	Unstressed, median (IQR)	Stressed, median (IQR)	*P*	Unstressed, median (IQR)	Stressed, median (IQR)	*P*
Intact (n=22)	1.1 (0.8 to 2.2)	1.3 (0.8 to 2.1)	.61	1.7 (1.4 to 2.0)	2.0 (1.6 to 2.3)	**.001**
AITFL (n=7)	1.5 (1.0 to 3.5)	1.6 (1.0 to 4.0)	.73	2.5 (1.7 to 3.5)	2.5 (2.0 to 5.0)	.074
AITFL+IOL (n=7)	1.8 (1.6 to 4.5)	2.1 (1.0 to 3.5)	.60	2.7 (2.1 to 4.2)	2.9 (2.6 to 5.0)	.445
PITFL (n=7)	1.1 (0.7 to 1.6)	1.2 (0.6 to 1.8)	.93	1.6 (1.2 to 2.2)	1.7 (1.4 to 2.3)	**.031**
PITFL+IOL (n=7)	1.4 (1.0 to 2.0)	1.6 (0.8 to 1.9)	.67	1.7 (1.6 to 2.3)	2.2 (1.8 to 2.5)	**.031**
DL (n=8)	1.5 (1.1 to 2.1)	1.5 (0.9 to 2.3)	.94	2.1 (1.8 to 2.5)	2.5 (2.2 to 2.8)	.232
DL+AITFL (n=8)	2.1 (1.0 to 2.9)	1.8 (0.9 to 3.1)	.79	2.5 (2.3 to 3.1)	2.6 (2.2 to 3.1)	.552
DL+AITFL+IOL (n=8)	2.1 (1.5 to 3.9)	2.1 (1.1 to 3.4)	.61	2.3 (2.3 to 3.6)	2.9 (2.4 to 3.3)	.672
AITFL+IOL+PITFL (n=14)	2.1 (1.6 to 4.0)	2.0 (1.3 to 4.6)	.87	2.6 (1.9 to 2.9)	3.1 (2.3 to 4.0)	**.001**
AITFL+IOL+PITFL+ DL (n=22)	2.2 (1.5 to 4.7)	2.0 (1.4 to 4.0)	.93	2.9 (2.3 to 3.7)	3.4 (2.7 to 5.2)	**.003**

Note: Median and interquartile range (IQR) are expressed in millimeters.
Significant P values (P < .05) are in bold.
Abbreviations: AITFL, anterior-inferior tibiofibular ligament; IOL, interosseous ligament; PITFL, posterior-inferior tibiofibular ligament; DL, deltoid ligament.

2

Francisco Acevedo, MD, Surgery - Surgical Oncology

Using Machine Learning and Natural Language Processing to Predict Cancer Risk after Multi-Gene Panel Testing

H. Kim[4], Y. Wang[1,2], D. Braun[5,6], F. Acevedo[1,3], C. Wang[5], Z. Deng[1], V.D. Armengol[1], N. Ouardaoui[7], G. Parmigiani[5,6], R. Barzilay[4] and K. Hughes[1]
[1]Surgical Oncology, MGH, Boston, MA, USA, [2]Breast Surgery, Shanghai Cancer Hospital of Fudan University, Shanghai, China, [3]Hematology-Oncology, Pontificia Universidad Catolica de Chile, Santiago, Chile, [4]Computer Science and Artificial Intelligence, MIT, Boston, MA, USA, [5]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA, [6]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA, USA and [7]College of Liberal Arts, Tufts University, Medford, MA, USA

Introduction: The use of next generation sequencing presents a tremendous opportunity in oncology allowing for the evaluation of cancer predisposition syndromes and identification of high-risk patients. ASK2ME (All Syndromes Known to Man Evaluator) is a risk prediction tool, which predicts the absolute risk of developing cancer for germline mutation carriers using evidence-based resources. Keeping the ASK2ME risk prediction tool up-to-date is challenging because new evidence appears in the literature every day, and the number of studies on gene cancer associations is constantly growing.

Methods: In this work, we develop an algorithm using machine learning and natural language processing (NLP) technologies to constantly scan medical literature for relevant studies as well as extract data from these studies. More specifically, we developed algorithms that take as an input XML abstracts from a PUBMED search (or any other search) and identifies relevant studies on germline genetic mutations and cancer associations. We created a training set by performing PUBMED searches on the following genes; MLH1, MSH2, MSH6, PMS2, VHL and p53. Five human annotators created manually annotated this training set which included over 1200 abstracts and identifying relevant abstracts. The machine learning NLP algorithm was trained on these abstracts and validation was performed on independent sets of abstracts.
Results: PUBMED queries for a specific gene cancer association identified on average 174 studies, of which the algorithm identified around 10% as relevant. The accuracy of NLP in identifying relevant abstracts was above 80%.
Conclusion: These algorithms enable us to constantly identify new studies, and ensure that the ASK2ME risk prediction tool is up-to-date, which is crucial as patients rely on the tool to obtain accurate risk estimates. Although these algorithms were developed in the context of identifying relevant papers on germline mutations and cancer risk associations, they can be extended to other settings as well and are more widely applicable.

3

Tomer Adar, MD, Medicine - Gastroenterology

A universal screening program that combines endometrial and colon cancers increases the detection of Lynch syndrome

T. Adar[1], L.H. Rodgers[2], K.M. Shannon[2], M. Yoshida[1], T. Ma[1], A. Mattia[3,4], G.Y. Lauwers[3], A.J. Iafrate[3], N.M. Hartford[3], E. Oliva[3] and D.C. Chung[1,2]

[1]Gastroenterology unit, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, [2]Center for Cancer Risk Assessment, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA, [3]Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA and [4]Department of Pathology, North Shore Medical Center, Danvers, MA, USA

Introduction: Lynch syndrome (LS) is the most common hereditary cause of both colorectal and endometrial cancers (ECs). Screening of all colorectal cancers (CRCs) for LS is currently recommended but routine screening of ECs remains controversial. We sought to determine the impact of screening all ECs in addition to CRCs in detection of LS.
Methods: An immunohistochemistry (IHC)-based screening program of all newly diagnosed CRCs and ECs was initiated in 2011 and 2013, respectively. Genetic testing was recommended for cases with absent MSH2, MSH6 or PMS2 staining, and for cases with absent MLH1 staining that did not exhibit a BRAF mutation and *MLH1* promoter methylation. Amsterdam II criteria (A-II), revised Bethesda criteria (R-BC), and $PREMM_{1,2,6}$ scores were ascertained in LS patients.
Results: 1290 CRC and 484 EC cases were screened for LS. Genetic testing was recommended for 137 CRC and 32 EC patients (10.6% and 6.6%, respectively; p=0.01). Overall, LS was identified in 24 unique individuals (1.4%), comprising 16 CRC and 8 EC patients (1.2% and 1.7%, respectively; p=NS). Among the subset of patients for whom genetic testing was recommended, the rate of LS diagnosis was significantly higher among EC patients (25.0% vs. 11.7%, p=0.052). The A-II, R-BC, and the $PREMM_{1,2,6}$ calculator would have missed 62.5%, 50.0%, and 12.5% of the identified LS patients, respectively.
Conclusion: Screening of ECs in addtion to CRCs is superior to screening of CRCs alone, significantly increases the number of unique LS families identified, and identifies families missed by clinical calculators. A universal screening program for LS should include both CRC and EC. **Disclaimer:** Dr. Lauwers has received consulting fees from Inspirata and Nine Point. Dr. Iafrate has received royalties from ArcherDx.

4

Oluwakemi Adegoke, MD, Emergency

Patient perceptions and experiences subsequent to emergency and essential operative procedures supported by a ketamine package, when no anesthetist was available, in rural Kenya

O. Adegoke[1,3,2], S. Villegas[1,2], B. Nelson[1,4,2] and T. Burke[1,3,4]

[1]Division of Global Health and Human Rights, Boston, MA, USA, [2]African Institute for Health Transformation, Luanda, Kenya, [3]Harvard T.H. Chan School of Public Health, Boston, MA, USA and [4]Harvard Medical School, Boston, MA, USA

Introduction: Five of the 7.3 billion people on earth do not have access to emergency and essential operations in a timely fashion. Lack of access to safe, affordable and timely anesthesia services, called the “anesthesia gap”, is one of the primary barriers to universal surgical coverage. The authors previously designed a solution to fill this gap when no

anesthetist is available, called every second matters for emergency and essential surgery – ketamine (ESM-Ketamine™). The ESM – Ketamine package includes a defined clinical pathway, complemented by wall charts, checklists, and ESM-Ketamine kits, for use when no anesthetist is available. Over the past four and half years mid-level and higher non-anesthetist providers have undergone 5-day training programs on the ESM-Ketamine pathway, and thereafter have supported emergency and essential operative procedures at their home facilities, when no anesthetist was available. The goal of this study was to assess patient experiences with ketamine after use in support of emergency and essential operative procedures when no anesthetist was available.

Methods: Interview guides were developed in an iterative fashion, building on validated published post-anesthesia assessment tools. Several trial assessments were performed in order to gain the eventual mature guide. The study population was a convenience sample (at times that the investigators were in-country) of patients age 18 or above who underwent operative procedures supported by ESM-Ketamine at the Sagam Community Hospital in Luanda, Kenya. Enrolled patients underwent two semi-structured interviews post-ketamine operative procedures. Patients were excluded if unable or unwilling to undergo interviews. Each enrolled patient underwent a guided interview subsequent to the operative procedure (prior to discharge), and a second interview between four to six weeks post-operation.

Results: Forty-seven patients were enrolled between January 16, 2017 and March 27, 2017. Mean patient age was 39 (range 22 – 71), 47 (100%) of whom underwent the first interview and 37 (78.7%) who additionally completed the second assessment. Thirty-nine (83.0%) of 47 in the first interview and 32 (86.5%) of 37 in the second reported that their experience with ketamine was "a positive one". Twenty-eight (75.7%) of the 37 patients who completed both interviews considered their "experience with ketamine positive" during both of their interviews. Two (5.4%) of the 37 patients who had reported a positive experience with ketamine on their first interview reported a negative experience in the second interview. In the first interview, 45 of 47 (95.7%) reported feeling no pain between the time of "falling asleep and awakening", 24 (51.1%) reported not remembering anything, 12 (25.5%) reported hearing voices, six (12.8%) recalled hearing events of the procedure, four (8.5%) remembered feeling unable to move or breathe, and four (8.5%) described dreams such as seeing people, thinking about living or dying, and feeling the oxygen mask. In the second interview, 37 (100%) of 37 reported feeling no pain between the time of "falling asleep and awakening", 20 (54.1%) reported not remembering anything, eight (21.6%) remembered a feeling of being unable to move or breathe, seven (18.9%) recalled hearing voices, two (5.4%) remembered hearing events of the procedure, and one (2.7%) described being aware of the surroundings. Forty-five (96%) of 47 would recommend use of ESM-Ketamine to support an operative procedure to a friend during the first interview and 35 (95%) of 37 in the second interview.

Conclusion: The overwhelming majority of patients that undergo emergency or essential operative procedures supported by the ESM-Ketamine package appear to remember the surgeries as pain free, and good experiences that they would recommend to a friend. A significant minority of patients recall various sensory inputs such as hearing voices, dreaming of people, and others.

5

Daniel Albrecht, PhD, Athinoula A. Martinos Center for Biomedical Imaging

Peripheral and central immune activation in patients with chronic radicular pain

D. Albrecht[2,3], S. Ahmed[1], N. Kettner[4], R. Borra[5,6], J. Cohen-Adad[7,8], H. Deng[9], T. Houle[9], A. Opalacz[1], S. Roth[1], M. Vidal Melo[9], L. Chen[1], J. Mao[1], J. Hooker[2], M. Loggia[2] and Y. Zhang[1]

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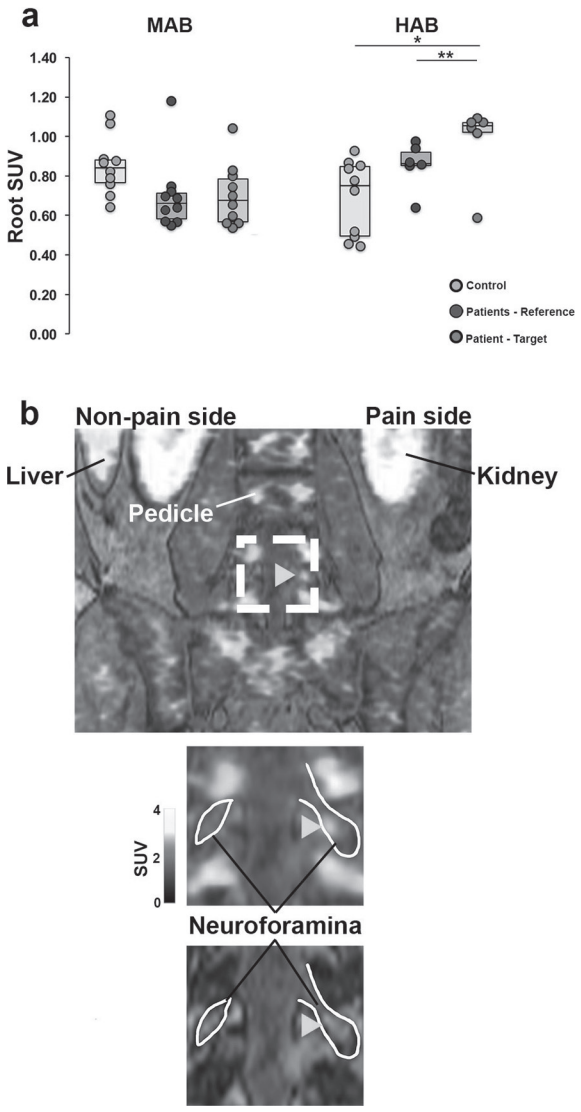
Introduction: Recent preclinical evidence indicated that neuroimmune signaling is an important contributor to the pathogenesis of persistent pain, occurring at multiple levels of the nervous system (e.g. in the peripheral and central nervous system). Despite substantial and growing animal evidence, however, the role of neuroimmune involvement in human chronic pain conditions remains uncertain. Here we assess inflammation in patients with sciatica and healthy controls with simultaneous positron emission tomography / magnetic resonance (PET/MR) imaging and [^{11}C]PBR28, a radioligand for the translocator protein (TSPO), which is upregulated in activated microglia and astrocytes, as well as macrophages. As such, [^{11}C]PBR28 imaging can assess both central and peripheral immunoactivation. We hypothesized that lumbar radiculopathy would be

associated with both peripheral and central immunoactivation, and that peripheral immune activation would be associated with response to anti-inflammatory epidural spinal injection (ESI).

Methods: 19 subjects with chronic lower extremity radicular pain lasting at least 3 months and 10 age and sex-matched healthy control subjects underwent study procedures. All subjects were genotyped for the Ala147Thr *TSPO* polymorphism which is known to affect binding affinity for [^{11}C]PBR28. Only High- or Mixed-affinity binders (HAB/MAB) were included. 60-90 minutes post-injection lumbar (for neuroforamen), and 90-110 minute thoracic (for spinal cord) PET images were acquired. Structural T1- and T2-weighted MR images were used for attenuation correction and anatomical localization of the PET images. T1 images were used for definition of target and reference regions-of-interest (ROIs). PET standardized uptake value (SUV) mages were computed by dividing Bq/mL by injected dose per body weight. **Statistical analysis**. We created a grouping factor ("region"): "target" region in patients (neuroforamen analysis – neuroforamen ipsilateral to symptomatic leg in the affected dermatome; spinal cord analysis – cord contained in T11-T12 vertebrae, which is connected to spinal nerves involved in lumbar radiculopathy), "reference" region in patients (neuroforamen analysis – neuroforamen contralateral to symptomatic leg in the affected dermatome; spinal cord analysis – cord contained in T7-T9) and healthy control region (neuroforamen analysis – left and right L5/S1 neuroforamen; spinal cord analysis – cord contained in T7-T9 and T11-T12). We used a subject-level random intercept in mixed effects models while assessing the fixed effect regional differences in PET signal in neuroforamen and spinal cord, controlling for *TSPO* genotype. Post-hoc comparisons were conducted with Bonferroni-correction.

Results: We first asked whether lumbar radiculopathy was associated with neuroforaminal immune activation (16 patients vs 10 controls). We found that addition of a region x genotype interaction to the model significantly improved the fit, and was included in the final model. The model revealed that, for high-affinity binders only, the "target" neuroforaminal PET signal in patients was significantly elevated relative to both the signal from the "reference" side in the same individuals, as well as signal in healthy controls (Fig. 1). A subset of patients (N=9) received ESIs during normal clinical care. We found that a positive response to ESI was observed only in patients with a ratio of target-to-reference SUV greater than 1 (i.e., target SUV > reference SUV; $p = 0.003$). We next asked whether radicular pain was also associated with spinal cord inflammation in a subset of patients (N = 9) and controls (N = 9). We found that target signal was significantly greater than both reference signal in patients as well as signal in healthy controls ($P < 0.001$, $P = 0.002$, Bonferroni corrected, respectively).

Conclusion: These findings suggest that immunoactivation of the nerve roots as well as glial activation in the central nervous system are key components of chronic radicular pain pathophysiology, and possibly a promising therapeutic target. In the treatment of chronic sciatica pain, besides targeting spinal nerve roots with ESI as in current clinical practice, central immune activation may also need to be therapeutically targeted, as indicated by numerous preclinical studies. Furthermore, the observed association between neuroforaminal inflammation and ESI response suggests that pre-selecting patients based on the presence and/or magnitude of neuroforaminal inflammation may improve overall treatment response. Large-scale studies are warranted to elucidate the relationship between these inflammatory signals and symptoms.



a) Regional differences in spinal root PET signal. *$P < 0.05$, **$P < 0.001$, Bonferonni corrected. **b)** Individual example of focal PET elevation of in the L4-L5 neuroforamen ipsilateral to the side of pain (green arrowheads), compared to unaffected, contralateral side. The hashed box in the top panel is enlarged in the middle (PET overlaid on MR) and bottom (MR only) panels.

6

Ayman Ali, BS, Medicine - Gastroenterology

Cost Effectiveness of a Novel Device for Improving Resuscitation of Apneic Newborns

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Introduction: Intrapartum-related hypoxic events are a major cause of morbidity and mortality in low resource countries. Neonates who receive proper resuscitation may go on to live otherwise healthy lives. However, even when a birth attendant is present, these babies frequently receive suboptimal ventilation with poor outcomes. The Augmented Infant Resuscitator (AIR) is a low-cost, reusable device designed to provide birth attendants real-time objective feedback on measures of ventilation quality during resuscitations and is intended for use in training and at the point of care. The goal of our study was to determine the long-term impact and cost-effectiveness of AIR deployment compared to current care in low resource settings.

Methods: We developed a computer-based simulation model of the natural history of intrapartum-related neonatal hypoxia and resuscitation deriving parameters from published literature and model calibration. Model simulations estimated the number of disability-adjusted life years (DALYs) averted with use of the AIR by birth attendants if deployed at the point of care. Potential decreases in neonatal mortality and long-term subsequent morbidity from disability were modeled over a life time horizon. The primary outcome for the analysis was the cost per DALY averted.
Results: Compared to current care, implementation of the AIR strategy resulted in a favorable cost of $40.44 ($8.13 – $133.14) per DALY averted. The findings were robust to sensitivity analyses. Ranges reflect lower and upper bounds based on uncertainty in model structure.
Conclusion: Our modeling analysis finds that real-time feedback on resuscitation quality may lead to a reduction in neonatal mortality and may be cost-effective in many low resource settings. Our data will hopefully lead to field tests of the AIR device and confirm our findings.

Results of the Base Case and Sensitivity Analyses

Parameter	Direction	Value	Cost per DALY Averted
Base Case	N/A	N/A	40.44 (8.13, 113.14)
Proportion of Time of Leaking with AIR	Lower	0.100	13.76 (3.15, 36.79)
Midwifes per Patient	Upper	0.010	84.18 (15.89, 285.71)
	Lower	0.003	20.61 (4.06, 62.88)
Increase in Cost with AIR	Upper	631.800***	452.13 (83.58, 2844.01)
	Lower	31.590***	19.63 (4.01, 82.22)
Probability of Apnea at Birth	Upper	0.109	19.94 (3.98, 51.84)
	Lower	0.027	82.78 (15.17, 287.07)

Key: DALY (Disability-Adjusted Life Year), AIR (Augmented Infant Resuscitator)

*Costs are presented as a mean value and a lower and upper bound that reflect the range of uncertainty in the calibrated parameter sets.

**The lower estimate indicates greater reduction of the time spent leaking when using the AIR device.

***Costs.

The Augmented Infant Resuscitator (AIR) Device

7

Elizabeth Allen, Performance Analysis and Improvement/Practice Improvement

Post-Epic Ambulatory Immunization Task Force

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Introduction: During the Clinical rollout and implementation of Partners eCare at MGH, there was an increase in tickets and safety reports relating to views, missing/duplication immunization and RN documentation. In order to address these safety issues an Immunization Tiger Team was formed out of the Epic Daily Safety Huddles. The number of MGH immunizations documented in the Epic immunization screen highlights the importance of this intervention. Between 1/2016 through 12/2016 : -Over 140,000 immunization administered in 119 MGH Ambulatory Epic Departments -Over 13,000 flu shots through the MGH flu clinic, with approximately 50% administered to patient ≤18 years old
Methods: The multidiscplinary team worked to identify a comprehensive list of post go-live immunization issues, established a plan to address the issues with the involvment of frontline providers/staff/leadership, provided oversight and implementation of the plan and transitioned unresolved and ongoing topics to permanent groups. Of the several issues identified, two of the main priorities of the task fell into the following categories: -Accuracy of the Epic Immunization Record -Provider Ordering and Clinician Workflows The Task Force, along with the Project Director for Clinical eCare implementation, worked to catalogy and then escalate inaccuracies in Epic Immunization records due to converstion issues from legacy systems and interfaces. There was immunizations missing from Epic, but displaying in legacy systems. There was duplicate immunization records that originated from seperate legacy systems and were converted into Epic. There was an undertermined amount of immunizations marked as “unknown” in legacy systems converted to “deferred” in Epic. Lastly, there were immunizations native to Epic overwritten by legacy interfaces that needed to be cleaned up. The Task Force addressed two primary issues relating to immunization ordering and documentating. The first, “Can we improve provider ordering efficiency and workflow?” and the second, “Can we improve nurse documentation of immunizations once ordered?”. The multidisciplinary team worked with providers and nurses to develop best practice recomendations as well as improvement recomendations to the Epic immunization screens.
Results: The Immunization Task Force esclated the safety issues associated with the inaccuracies in Epic Immunzation records to Partners eCare. The issue is still being addressed, but at the Partners level. In the Spring of 2017, Partners eCare

issued an Immunization Safety Alert asking clinicians to **Review immunizations in the LMR Summary** (available within the PHS viewer) and compare them to the immunizations documented in the Epic immunizations activity, and to **Review immunization history with patients and their caregivers whenever possible**. The Task Force convened several Phyisican leaders to determine provider ordering recommendations, including: placing future immunization orders, smart grouping/ thoughful preference list, and using expected dates/expiration dates. Further, the group proposed considering the Immuization Coalition Standing Orders for use as Protocol orders at MGH. These orders would require provider approval, but approval could occur after administration. The Task Force mapped and analyzed the nursing workflow in several pediatrics and one adult practice. The results indicated that shadow paper systems existed, vaccines are not always ordered prior to visit (RNs had to find MDs to order), and RNs did not consistently have access to computers in the exam rooms to document immunizations. These findings supported the importance of provider ordering best practices. In addition, the team worked on improving the nursing documentation workflow in Epic. Work was completed with the eCare team to update the documentation screen in Epic to a more standard presentation, each documentation follows the same order and offers the same questions for documentation.
Conclusion: The Post-Epic Immunization Task Force addressed more than 20 issues assocated with the Epic Immunization record. The four main priorities of work included: - Immunization Records in Epic - Provider Ordering and Clinician Workflows - Flu Vaccine Clinics - Communication and Training The multidiplinary nature of the task force was key to accomplishing the spread of work. The next phase of the task force includes transitioning oversight of MGH immunization topics going forward.

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Renata R. Almeida, MD, Radiology

Radiology in the Midst of the Opioid Epidemic: 12-year Analysis of Imaging Findings, Mortality and Opioid Prescription History among Patients with Intravenous Substance Use Disorders (IV-SUDs) Presenting to Emergency Radiology

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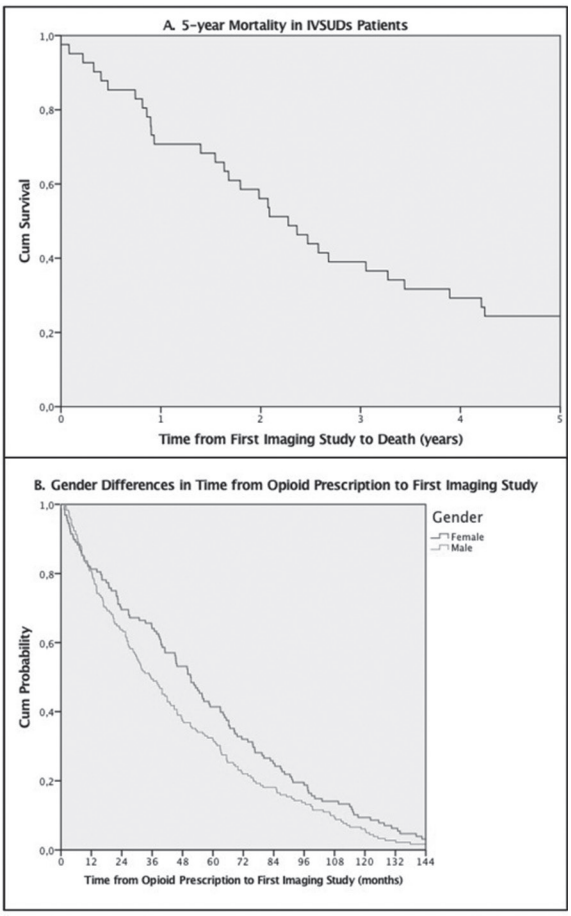
Introduction: To assess the prevalence and type of IV-SUDs imaging complications, mortality rate, and history of opioid prescriptions (OP) and in patients presenting to Emergency Radiology (ER).
Methods: HIPAA compliant-IRB approved retrospective study of 1031 patients who presented to ER (2005 to 2016) to assess IV-SUDs complications. Demographics, clinical symptoms, imaging diagnosis, history of OP, and dates of death were recorded. Exams were categorized by imaging diagnosis, modality and specialty. Analyses for significant differences were done.
Results: In 1031 patients (65% men; mean age 36 yrs; 78% white; 95% English speakers), 1673 exams (779 X-rays, 544 CT, 292 MRI and 58 US) were performed (1-13 exams per patient, mean 1), accounting for 0.2% (1673/854299) of all ER studies in the same period. 52% of patients had 1 or more studies with IV-SUDs complications. The rates of positive imaging per imaging specialty were: GI 77% (113/146), MSK 52% (419/802), Vascular 48% (77/162), Neuro 47% (97/206), and chest 25% (90/356). Most frequent clinical symptoms were local complications of injections (27%, 450/1673), respiratory (15%, 251/1673) and back pain (13.4%, 224/1673). History of OP before the first imaging was present in 30% (310/1031) of cases (mean 10 prescriptions per patient); significantly more often in women (37%, 128/348), than men (27%, 182/673, p=0.008). Mean time from OP to first imaging was 51 months (SD 39); significantly shorter in men (45 months) than women (51 months, p=0.01). Overall death was recorded in 11.7% (121/1031) of patients; significantly higher in patients with positive imaging diagnosis of IV-SUDs complications (14%, 73/534) than in those without (10%, 48/449, p=0.04). 5-yr mortality rates were: 7% (73/1031) overall; higher in patients with prior opioid prescription (9%, 29/310) than in those without (6%, 44/721, p=0.06); higher in patient with imaging complications (6%, 33/534) than in those without (4%, 21/427, p=0.2).
Conclusion: There is a high prevalence of multisystem IV-SUDs imaging complications among patients presenting to the ER. Patients with positive imaging findings and prior OP have a higher overall mortality rate compared to patients with negative imaging.



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Mohamad J. Alshikho, MD, Neurology

Imaging glial activation in people with Amyotrophic Lateral Sclerosis (ALS)

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Introduction: [^{11}C]-PBR28 is a second generation radioligand that binds to translocator protein (TSPO) expressed on activated glial cells. We have previously shown preliminary *in vivo* evidence of increased glial activation in the motor cortex (MC) in people with amyotrophic lateral sclerosis (ALS). Here, we confirm our initial finding, study the longitudinal changes, and characterize the gray-white matter distribution of glial activation in a large cohort of ALS and primary lateral sclerosis (PLS) participants.

Methods: Fifty-three ALS, eleven PLS and twenty-one healthy control (HC) participants underwent simultaneous MR-PET imaging using [^{11}C]-PBR28. Demographics and clinical assessments including upper motor neuron burden (UMNB) and the revised ALS functional rating scale (ALSFRS-R) were collected. [^{11}C]-PBR28 uptake was quantified as standardized uptake value ratio (SUVR), and compared between groups using voxelwise, surface-based, and region of interest (ROI) analyses. Cortical thickness (CT), fractional anisotropy (FA) and SUVR were compared between the groups and correlated with the clinical measures. [^{11}C]-PBR28 uptake, FA, and CT were compared over six months in ten ALS subjects who completed follow-up scans.

Results: Voxelwise, surface-based and ROI analyses revealed increased [^{11}C]-PBR28 uptake in the MC in ALS participants compared to HC (P_{FWE}<0.05, P_{CW}<0.05, P<0.05; respectively). The increase in [^{11}C]-PBR28 uptake co-localized and correlated with decreased CT (r= - 0.49; P<0.05) and reduced FA (r= - 0.56; p<0.05). Glial activation correlated with higher UMNB (r=0.53, P<0.05) and lower fine motor domain of ALSFRS-R (r= -0.33; P<0.05). There was no correlation between [^{11}C]-PBR28 uptake and disease duration, or rate of progression. The correlation of [^{11}C]-PBR28 uptake in the MC at baseline and six months was (r= + 0.84; P=0.0022). [^{11}C]-PBR28 uptake was predominantly increased in the in sub-cortical white matter of the MC in the PLS group (P_{FWE}<0.05).
Conclusion: [^{11}C]-PBR28 uptake is increased in the MC in people with ALS and PLS, co-localizes with structural abnormalities, and correlates with relevant clinical measures. [^{11}C]-PBR28 uptake is remarkably stable over six months despite ALS progression. [^{11}C]-PBR28 PET is a promising candidate molecular biomarker to measure the impact of experimental treatments on glial activation in future ALS clinical trials.

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Rachel Alvarado, Radiology

Choice Reaction Time and Implicit Learning Deficits in Older Adults with Mild Cognitive Impairment

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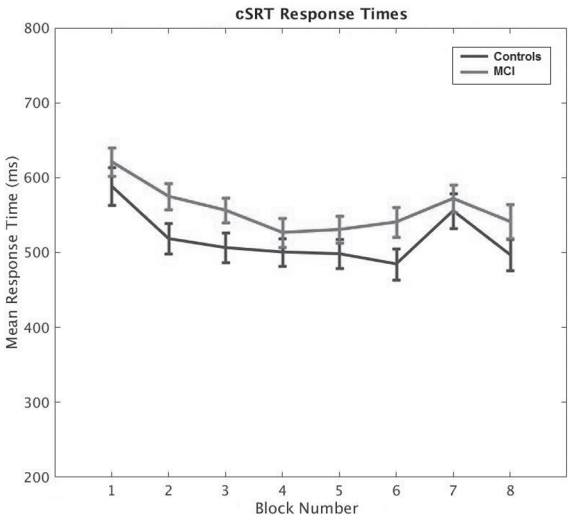
Introduction: Mild cognitive impairment (MCI) refers to a condition common in older adults where cognitive abilities are attenuated relative to cognitively healthy older adults but these deficits do not have a substantial impact on daily living and functional independence. Individuals with MCI are at greater risk for a future diagnosis of Alzheimer's disease (AD) and so MCI is studied to better understand disease processes in the earliest stages of symptom expression. Typically, a diagnosis of MCI is determined based on performance on neuropsychological tests that assess memory, attention, language and executive function. More complex tests of cognitive function are thought to be necessary to highlight subtle deficits in individuals with MCI, but little is known about how individuals with MCI perform more simple tasks such as choice reaction time as well as typically preserved functions such as implicit learning.
Methods: We examined performance on a choice/serial reaction time (cSRT) paradigm in a group of neuropsychologically defined MCI and a group of cognitively healthy older adults (CHOA). For the cSRT task, the computer screen displayed four outlined boxes to the participant that would flash one at a time in a pseudo-random order ('random' blocks) or repeated order ('repeated' blocks). Participants were instructed to press the spatially corresponding button on the 4-choice button box to the box that flashed on the screen as quickly as possible without sacrificing accuracy. The task comprised of 8 blocks alternating pseudo-random (24 items) and repeated (12 items, repeated 6 times) sequences. All participants performed the task uninformed of the embedded pattern or of transitions between blocks.
Results: MCI had slower reaction times to the first random block, showing impaired performance in the simple choice reaction time portion of the task. MCI had slower reaction times across all blocks, as well as reduced sequence learning (difference in reaction times between the random and repeated blocks). A potential interference effect after implicitly learning the embedded pattern was present in both groups represented by substantial increases in reaction times for both groups in the last random block followed by regained performance during the last repeated block.
Conclusion: These results suggest that individuals with MCI already exhibit deficits on simple tests of perceptual-motor performance. This study was funded by the NIH and was carried out by the Athinoula A. Martinos Center for Biomedical Imaging at the Massachusetts General Hospital, using resources provided by the NIH grants R01NR010827, NS042861, NS058793 and by the Center for Functional Neuroimaging Technologies, P41RR14075. Participant enrollment and clinical diagnosis was conducted with help from the Massachusetts Alzheimer's Disease Research Center.



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Raza M. Alvi, MD, Radiology

Systolic Heart Failure and Adverse Heart Failure Outcomes Among Persons Living with HIV

R.M. Alvi[1], M. Afshar[2], N. Tariq[3], J. Gerber[3], V. Triant[4], M. Zanni[5] and T.G. Neilan[4]

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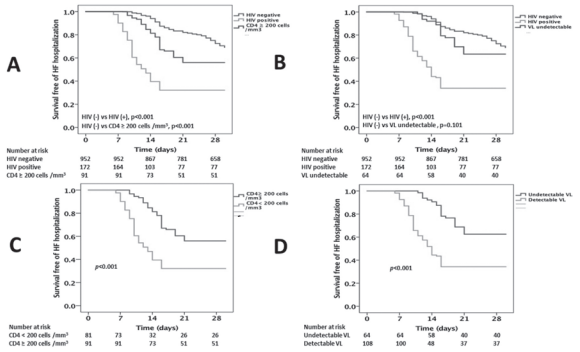
Introduction: Persons living with HIV (PLHIV) have an increased risk of heart failure with a reduced ejection fraction (HFrEF). However, little is known about outcomes among PLHIV hospitalized with HFrEF. In this study, we sought to compare HF outcomes among PLHIV hospitalized with HFrEF vs. individuals without known HIV (non-HIV-infected individuals) hospitalized with HFrEF.

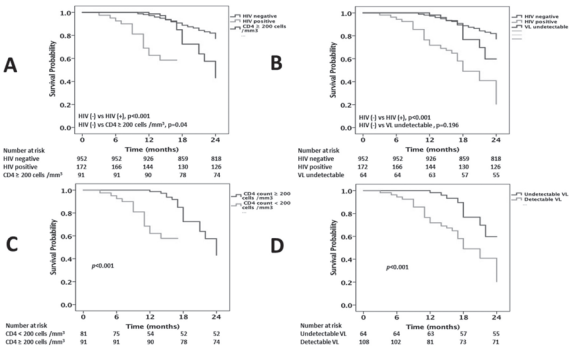
Methods: Our studied cohort included 1,124 individuals admitted to a US tertiary care hospital in 2011 with decompensated heart failure and an LVEF of <50%. Fifteen percent of these individuals (172/1,124) had a concomitant diagnosis of HIV. Amongst PLHIV hospitalized with HFrEF vs. non-HIV-infected individuals hospitalized with HFrEF, we compared baseline characteristics, 30-day HF readmission rate (primary outcome), and cardiovascular (CV) and all-cause mortality (secondary outcomes). Within the group of PLHIV hospitalized with HFrEF, we also assessed outcomes stratified by CD4 count ≥ or <200 cells/mm^3 and by suppressed or non-suppressed viral load (VL). Finally, in the group with HIV, we examined both traditional and HIV-specific parameters associated with 30-day HF readmission rate.

Results: Amongst PLHIV hospitalized with HFrEF vs. non-HIV-infected individuals hospitalized with HFrEF, there were no significant differences in age, sex, race, or traditional CV risk factors. The LVEF was comparable between groups, but amongst PLHIV, pulmonary artery systolic pressure was higher and there was an increased prevalence of cocaine use. In follow-up, PLHIV hospitalized with HFrEF had a higher 30-day HF readmission rate (55% vs. 30%, p< 0.001), as well as an increased CV mortality (27% vs. 14%, p< 0.001) and all-cause mortality (41% vs. 26%, p< 0.001). Among PLHIV hospitalized with HFrEF, those with a lower CD4 count (<200 cells/mm^3 vs. ≥200 cells/mm^3) had a higher 30-day HF readmission rate (68% vs. 44%, p< 0.001), and higher rates of CV (36% vs. 19%, p< 0.001) and all-cause (54% vs. 29%, p< 0.001). mortality. Analogously, those with a detectable VL (>50 vs. ≤50 copies/ml) had a higher 30-day HF readmission rate (65 vs. 37%, p< 0.001), and higher rates of CV (34% vs. 14%, p< 0.001) and all-cause mortality rate (53% vs. 20%, p< 0.001). Finally, in the group with HIV, both traditional HF RF (e.g. history of CAD, use of standard HF medications), non-traditional HF RF (e.g. cocaine use), and HIV-specific risk parameters (e.g. CD4 count, viral load) were independent predictors of 30-day HF readmission rate.

Conclusion: PLHIV hospitalized with HFrEF have increased 30-day HF readmission rates and increased rates of CV and all-cause mortality as compared with non-HIV-infected individuals hospitalized with HFrEF. Adverse outcomes among PLHIV hospitalized with HFrEF are more common among those with CD4 <200 cells/mm^3 and/or detectable viral loads



Kaplan Meier survival curves comparing the 30-day readmission among (A) PLHIV and uninfected controls and PLHIV with a CD4 count ≥200 cells /mm^3, (B) PLHIV and uninfected controls and PLHIV with an undetectable viral load (<50 copies/ml), (C) PLHIV with a CD4 ≥200 cells /mm^3 vs. patients with CD4 count <200 cells /mm^3, (D) PLHIV with an undetectable viral load with those with a detectable viral load



Kaplan Meier survival curves comparing cardiovascular mortality among (A) PLHIV and uninfected controls and PLHIV with a CD4 count ≥200 cells /mm^3, (B) PLHIV and uninfected controls and PLHIV with an undetectable viral load (<50 copies/ml), (C) PLHIV with a CD4 ≥200 cells /mm^3 vs. patients with CD4 count <200 cells /mm^3, (D) PLHIV with an undetectable viral load with those with a detectable viral load.

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Sophia E. Anderson, Orthopedics

Risk factors for adverse events after intra-articular corticosteroid injections in the ankle and hindfoot

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Introduction: Little data exists regarding the rate of adverse events, nor any associated risk factors, after intra-articular corticosteroid injections in the ankle and hindfoot. The aim of this study was to determine the complication rate associated with such injections, as well as identify any predictive risk factors.

Methods: A retrospective database was created using adult patients who had received an ankle or hindfoot injection between January 2000 and April 2016 at one of three hospitals, including two Level I trauma centers, using Current Procedural Terminology codes correlating to injection into an intermediate joint. Only patients without prior intra-articular injection of corticosteroid into the ankle or subtalar joint were included. Explanatory variables were defined as sex, age, race, body mass index, diabetes status, tobacco use, presence of fluoroscopic guidance, location of injection, and administering physician's years of experience.

Results: Out of 1708 patients in the final cohort, 99 patients (5.8%) had an adverse event. The most prevalent types of adverse events were post-injection flare (4.5% of total cohort) followed by skin reaction (0.5% of total cohort). There were two tendon ruptures and no infections noted. Bivariate analysis identified significant risk factors ($p < 0.05$) to include female patients (P=0.03) and subtalar location of injection (P=0.017). Multivariable logistic regression analysis highlighted that the subtalar joint (P=0.004) was independently associated with development of an adverse event.

Conclusion: The rate of adverse event after ankle or hindfoot corticosteroid injection was 5.8%, with post-injection flare being the most common event. Injection into the subtalar joint was independently associated with the development of an adverse event after intra-articular corticosteroid injection, and this was not mitigated by the use of fluoroscopic guidance.

Table I: Incidence of Adverse Events

Adverse Event	No. (%)
Post-injection flare	78 (74)
Vasovagal reaction	7 (7)
Facial flushing	6 (6)
Spontaneous tendon rupture	2 (2)
Skin reaction	10 (9)
Temporary numbness	2 (2)
Temporary increase in blood sugar	1 (1)
Total	106

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Sheeba Anteraper, Psychiatry

A data driven approach to understanding atypical functional connectivity in adults with High-functioning Autism Spectrum Disorder

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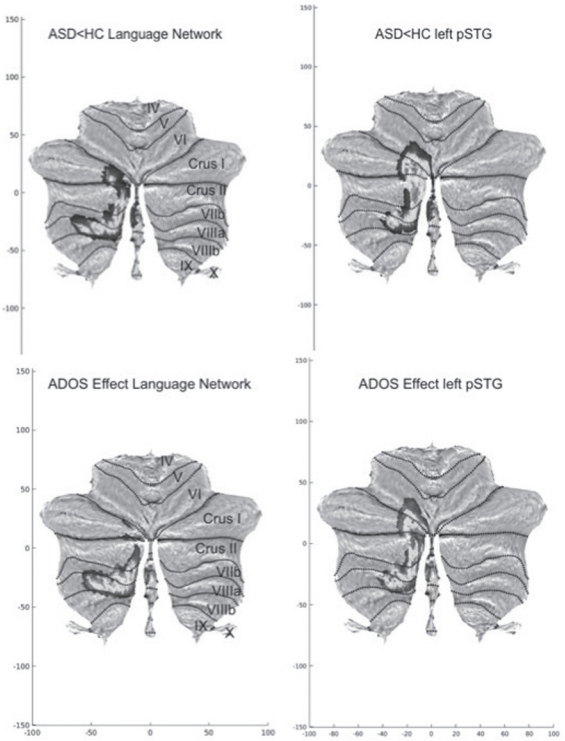
Introduction: A recent review of resting-state functional connectivity MRI (rs-fcMRI) studies in Austism Spectrum Diorder (ASD) reveals both over- and under-connectivity in ASD [1]. While majority of such investigations were carried out with an apriori hypothesis, posing a limit to the number of brain regions examined, we aimed to follow an unbiased whole-brain data-driven approach to look for potential rs-fcMRI differences between typically developing healthy controls (HC) and those with high-functioning ASD (HF-ASD).

Methods: Connectivity analyses were carried out using CONN [2]. Whole-brain networks (Default Mode Network (DMN), Sensorimotor, Visual, Salience/Cingulo-Opercular, DorsalAttention, FrontoParietal/Central Executive, Language, and Cerebellar) derived from Independent Component Analyses (ICA) on the Human Connectome Project (HCP) data set were used for functional connectivity analyses on the open-access ABIDE dataset (Autism Brain Imaging Data Exchange; N=59; 35 HC and 24 ASD). Detailed information is provided in the release/website (http://fcon_1000.projects.nitrc.org/indi/abide/). Resting scan images were obtained on 3T Siemens Skyra (TR=0.475s, TE=30ms, flip angle=60°, 3x3x3 mm^3 voxels, Multiband factor of 8, 947 time points). Prior to connectivity analysis, data were realigned, normalized, spatially smoothed with a 6-mm kernel using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK). Band pass filtering was executed at 0.008-0.1 Hz. Physiological sources of noise (signals from white matter and cerebrospinal fluid) were regressed out together with movement related covariates and motion outliers (scan-to-scan threshold of 0.5 mm). Correlation coefficients were converted to normally distributed scores using Fisher's r-to-z transform to allow for second-level analyses. Cerebellum clusters were visualized using the SUIT toolbox [3]. Although there was no significant difference in the total number of valid scans per group, since the maximum head movement in the ASD group was significantly more compared to the ASD group, we have regressed out the effect of maximum motion in the second-level analyses.

Results: Of the networks examined, only the language network stood out as statistically significant for the between group comparison as distinctly lower correlations between the language network and left cerebellum (Crus I, II and VII). Of the four regions of interest within the language network (bilateral inferior frontal gyrus and bilateral posterior superior temporal gyrus (pSTG)), the biggest contribution to the between group difference was from left pSTG. In addition, the correlation analysis between the clinical scores of autism (ADOS) and RsFc of the whole brain (on both language network and left pSTG) revealed significant inverse correlations with left cerebellar functional connectivity.

Conclusion: Using a synergistic combination of 32 Channel coil, simultaneous multi-slice and high-temporal resolution imaging, we provide evidence for cerebellar differences in HF-ASD within the language network. Several studies have hinted that ASD is a disease of the cerebellum [4, 5]. In our previous work on investigating DMN, cerebellum connectivity (left Crus I, II) was significantly positively enhanced in the HC group compared to HF-ASD [6]. Left Crus II has been suggested as a potential target for non-invasive brain stimulation based on its connectivity with the temporoparietal cortex [7] but the study did not use whole brain coverage and correlations with clinical scores were missing. Interestingly, perfusion (regional cerebral blood flow) abnormalities specifically within the left STG and inverse correlations with autism trait severity have been shown before [8]. pSTG differences pertaining to social deficits [9] or differences in mirror neuron system [10] within the ASD population have been reported. Our results suggest stronger functional connectivity differences between lpSTG and cerebellar regions in the HC group compared to ASD. Presence of strong inverse correlations in functional connectivity values with ADOS suggests that the proposed data driven approach is promising to come up with potential biomarkers and effective therapies in HF-ASD. **References:** [1] Hull et al., 2016. Frontiers in psychiatry. [2] Whitfield-Gabrieli et al., 2012. Brain connectivity. [3] Diedrichsen and Zotow, 2015. PLoS ONE. [4] Rogers et al., 2013. Front. Syst. Neurosci. [5] Wang et al., 2014. Neuron. [6] Joshi et al., Brain Connectivity. [7] Ingelstrom et al., 2017. Cerebral Cortex. [8] Meresse et al., 2005. Annals of Neurology. [9] Redcay et al., 2013. Human Brain Mapping. [10] Fishman et al., 2014. JAMA Psychiatry.



Between-group functional connectivity maps of language network and left pSTG (top panel) revealed significant differences in left cerebellar functional connectivity (ASD<HC contrast) and whole brain effect of ADOS scores revealed significant inverse correlations with left cerebellar functional connectivity. Height threshold = $p<0.001$, $p<0.05$ FWE corrected.

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Mykyta Artomov, PhD, Medicine - Analytic and Translational Genetics Unit (ATGU)

Rare Variant, Gene-Based Association Study Of Hereditary Melanoma Using Whole Exome Sequencing

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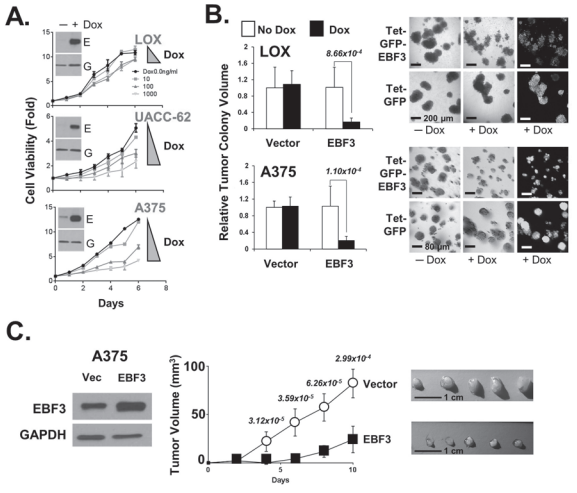
Introduction: Extraordinary progress has been made in our understanding of common variants in many diseases, including melanoma. However, the systematic pursuit of rare disease-causing variants is just emerging. Given the high cost of sequencing in the past, linkage analysis provided a robust method to leverage recombination for positional information. For relatively common endpoints, linkage has been largely unsuccessful as, beyond rare examples of single pedigrees that are sufficiently large and carry a near-fully penetrant mutation to generate statistically significant linkage, the polygenic nature of common disease precludes gene localization. To overcome the fact that rare variants are distributed across many genes, we and others have proposed methodologies for gene discovery through rare variant association studies. Here we performed largest up-to-date cohort-based rare variant association studies for cutaneous melanoma (CM) and ocular melanoma (OM).
Methods: Using 11,990 jointly processed cases and controls, whole exome sequencing was performed followed by large-scale joint variant calling using GATK. Plink/SEQ was used for statistical analysis of genetic variation. Four models were used to estimate association among different types of variants. In vitro functional validation was performed using 3 human melanoma cell lines in 2D and 3D proliferation assays. In vivo tumor growth was assessed using xenografts of human melanoma A375 melanoma cells in nude mice (8 mice per group). All statistical tests were two-sided.
Results: To ensure ancestral matching, we performed principal component analysis between the cases and control cohorts in both the primary and TCGA replication cohorts. Our analysis was then restricted to European cluster of samples only. We performed statistical analysis of the rare variation using composite multi-test model. Strong signals were detected for *CDKN2A* ($p=6.16\times10^{-8}$) in the CM cohort (n=273) and *BAP1* ($p=3.83\times10^{-6}$) in the OM (n=99) cohort. Eleven genes which exhibited borderline association ($p<10^{-4}$) were independently validated using the TCGA melanoma cohort (379 CM, 47 OM)

and a matched set of 3,563 European controls with *CDKN2A* (p=0.009), *BAP1* (p=0.03) and *EBF3* ($p=4.75x10^{-4}$), a candidate risk locus, all showing evidence of replication. *EBF3* was then evaluated using germline data from a set of 132 familial melanoma cases and 4,769 controls of U.K. origin (joint $p=1.37x10^{-5}$). Somatically, loss of *EBF3* expression correlated with progression, poorer outcome and high MITF tumors. Functionally, induction of *EBF3* in melanoma cells reduced cell growth in vitro, retarded tumor formation in vivo, and reduced MITF levels (Fig. 1)

Conclusion: The design of our study incorporates several classic RVAS strategies though there are also several limitations. Full exome sequencing is still more expensive compared to genotyping but the costs are converging. Although we enriched for genetic causation by focusing on rarer familial and multiple tumor cases, statistical power is still lower than those reported for common variant GWAS. Recognizing this risk, we subjected all available cases to our analytical pipeline including the *CDKN2A* and *BAP1* families and were reassured that statistically significant association signals were readily detected for these loci. Despite limitations, the analyses in this report represent a major first step towards understanding the landscape of rare mutations in hereditary melanoma. The statistical methodologies which were blindly deployed in the case/control design unequivocally recovered several anticipated signals (i.e. *CDKN2A* and *BAP1*). Moreover, several sub-threshold loci have been nominated for future studies including a proof-of-concept validation of one such gene, *EBF3*.



Functional accreditation of EBF3. A) Cell viability assay demonstrating growth arrest of human melanoma cell lines with EBF3 upregulation by dose-depen- dent induction with doxcycyline; experiments were performed in triplicates (relative mean viability +/- SD) and independently replicated using three different cell lines (LOX, UACC 62, and A375). B) 3D spheroid formation is dramatically reduced by the induction of EBF3 (relative mean tumor colony size +/- SD). C) Constitutive overexpression of EBF3 in A375 cells led to a profound suppression of tumor growth in nu/nu mice (n=8 in each arm, mean tumor volume +/- SD). P values generated from two-sided t tests are shown above each time point. Five representative dissected tumors from each arm are also shown. Dox = doxycycline; Vec = vector.

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Jeffrey M. Ashburner, PhD, MPH, Medicine - General Internal Medicine

Value-Based Primary Care Outcomes: Validating an Algorithm for Incident Myocardial Infarction and Assessing Trends over 10 Years

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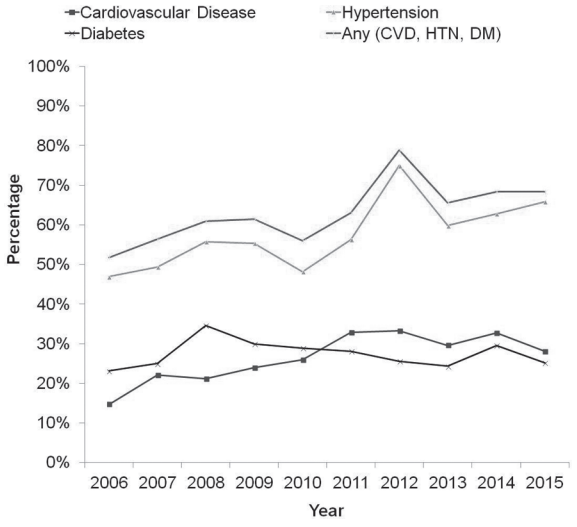
Introduction: Most primary care (PC) quality measures assess care processes or intermediate outcomes. Delivering value-based services requires assessing outcomes that directly contribute to health. We developed and validated an electronic algorithm to identify patients seen within a large PC network with incident myocardial infarction (MI); identified incident MIs over a 10 year period; and examined changes in prevalence of pre-existing chronic diseases over time.

Methods: The cohort includes adults aged 18+ with incident MI cared for in a 19-practice PC network between 2006-2015, a period when the network grew from 143,995 to 163,279 patients. We identified patients with an inpatient primary discharge diagnosis of MI or two outpatient visits with problem list terms or billing code diagnoses for MI. We excluded outpatient MI diagnoses identified in patients new to the network without an inpatient diagnosis to exclude prevalent events. We applied this algorithm to each calendar year. We randomly chose up to 2 cases per practice in each year (n=312) and 25 controls per practice (n=475) for chart review validation. Fifty randomly selected patients with newly diagnosed coronary artery disease (CAD) not identified as having a MI were assessed to identify missed incident events occurring outside our network.

A research nurse performed blinded electronic chart reviews. We assessed the number and proportion of patients with incident MI per year, and the proportion with established cardiovascular disease (CVD) (CAD, peripheral and cerebrovascular disease), hypertension, and diabetes before the incident MI. We examined trends over time using the Cochran-Armitage test.
Results: Chart review validation of 787 patients yielded a sensitivity of 96%, specificity of 91%, positive predictive value of 86%, and negative predictive value of 98%. Among 50 patients with a new CAD diagnosis without incident MI, 46 (92%) did not have a MI, while 4 (8%) had a MI. Of the 4, 2 occurred before joining the PC network, and 2 (4%) were incident MIs missed by the algorithm. Between 2006-2015, the annual in-network incidence of MI ranged from 0.09% (n=130 in 2009) to 0.13% (n=192 in 2011). The average age of MI patients was 67.5 years, and 65.6% were male. The proportion of MI patients with pre-existing CVD (14.7% in 2006, 28.1% in 2015) or hypertension (46.9% in 2006, 65.9% in 2015) increased over time (all $p<0.001$), while the proportion with pre-existing diabetes did not (23.1% in 2006, 25.2% in 2015; $p=0.8$). The proportion with any chronic condition increased from 51.8% in 2006 to 68.3% in 2015 ($p<0.001$) (Figure 1).
Conclusion: We developed and validated an outcome measure for incident MI in a PC network. Though rates of MI were stable, the percentage of patients with pre-existing chronic disease risk factors for MI increased over 10 years. The low incidence of MI in this large network suggests that composite measures which include multiple outcomes (e.g. MI and stroke) may be needed to accurately assess value-based PC quality.



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Mursal Atif, Medicine

Virtual PSA Monitoring Pilot Program

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Introduction: Prostate cancer is the most common non-skin cancer among American men and one of the leading causes of death among men of all races. Statistics from 2014 show that more than 100,000 men were diagnosed with prostate cancer and it was a cause of death for around 28,343 men. One of the most common screening methods is the prostate specific antigen (PSA) blood test but only a biopsy can confirm prostate cancer. Treatment options comprise active surveillance, surgery, radiation therapy and hormone therapy. Active surveillance via follow up visits after surgery and therapy is a major component of treatment protocol. However, this workflow limits the clinician's time for new patient consultations. Overall, prostate cancer clinics benefit from having a balance of consultations and automation of follow up visits. The aim of this project was to develop a proof of concept software platform to automate and coordinate patient care as well as act as a decision support tool for clinicians at a prostate cancer clinic. We used REDCap, a web application commonly used by research teams to manage participant enrollment, clinical measures and build online surveys. The flexibility of creating and deploying surveys and enabling calculations makes REDCap an appropriate platform. A Virtual PSA Monitoring (VPSAM) pilot program was initiated to test the feasibility of the program as a standard of care within the prostate cancer clinic.
Methods: A team of clinicians, REDCap developers and connected health experts designed the function and form of the platform. Upon completion of radiotherapy, patients who chose to participate in the VPSAM program were entered into the system - including their demographic information, cancer staging and treatment information. This information was used to

calculate a unique monitoring schedule based on risk level and PSA relapse category for each patient. Per monitoring schedule each patient was sent a validated AUA/EPIC-26 symptom survey before their PSA check visit and post visit survey. After each PSA check visit, clinical information was entered by the VPSAM administrator. A nurse practitioner would review clinical and symptom information before discussing the results with each patient. Marking this task complete triggered a post-visit survey to be sent to the patient.
Results: 278 patients were approached between March-September 2016 and 251 (90.2%) enrolled in the program. Post visit survey results showed that 98% of the patients strongly agreed/agreed that they understood their testing results.
Conclusion: The flexibility of the REDCap platform to evaluate clinical measures via logic calculations and summation of previous clinical information from the clinician eliminated the burden of manual calculations. Overall, this proof of concept project makes a case for the importance and need of software platforms that provide decision support for clinicians and proper record keeping for a high-volume prostate cancer clinic.

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Yanik J. Bababekov, Surgery

Market Competition Standardizes Liver Transplant Waitlist Management Practices

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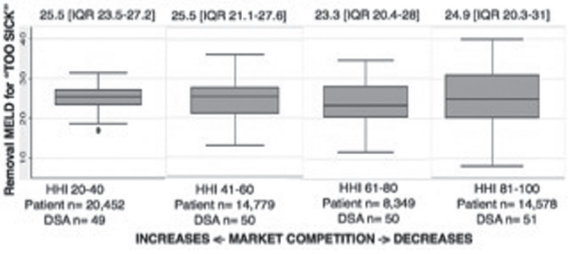
Introduction: Geographic inequity in liver transplantation has been previously characterized. However, waitlist management practices at the donor service area (DSA) level with respect to delisting for "too sick to transplant" (TS) are unknown. We hypothesized that non-medical factors predict removal Model for End Stage Liver Disease score (MELD) for TS.
Methods: We used Scientific Registry of Transplant Recipients data from 2002 to 2012 to analyze reason for delisting of a total of 58,158 adults on the liver transplant waitlist at active programs. We excluded non-liver transplanting DSAs, patients with malignancy, exception points, status 1 listing, and removal codes for error, other, refused transplant, and live donor liver transplant. Regression analysis assessed which medical and non-medical factors predict removal MELD at TS. Herfindahl-Hirschman Index (HHI) was utilized as a variable for market competition (MC).
Results: On adjusted analysis, less MC predicted higher MELD for TS. For every unit decrease in MC, the MELD for TS increased by 0.03 points. There is vast variation in MELD for the likely single center DSAs – or those without MC. F-test of equity of variances were significantly different between groups of HHI (all p <0.001). Single center DSAs delisted at MELDs for TS from 8 to 40; however, in highly competitive DSAs the definition of TS seems to standardize (all p <0.001) **(Figure 1)**.
Conclusion: The definition of TS varies most among single center DSAs and is influenced by non-medical factors. Nevertheless, in highly competitive DSAs, a single standard develops as variation in MELD for TS decreases with increasing MC. Thus, increased MC may be associated with more aggressive waitlist management practice patterns.

Figure 1. Market Competition Standardizes Removal MELD for "too sick to transplant".
HHI, Herfindahl-Hirschman Index; *DSA*, Donor Service Area



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Aymen Baig, Medicine - MGH Cancer Center

A Novel Rapid *IDH1*/*IDH2* Clinical Test Is Expanding Access of Newly-Diagnosed Heme Malignancy Patients to Clinical Trials Evaluating IDH1/2 inhibitors.

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Introduction: Isocitrate dehydrogenase 1 (IDH1) and IDH2 are enzymes in the citric acid cycle involved in glucose metabolism. Heterozygous mutations in the *IDH1* and *IDH2* genes have been identified in a specific subset of cancers. Mutations typically affect the enzyme's active site at codon R132 in the *IDH1* gene and R140 or R172 in the *IDH2* gene, conferring a neomorphic enzyme activity that produces the oncometabolite, 2-hydroxyglutarate (2-HG). 2-HG in turn promotes malignant transformation by interfering with the activity of epigenetic regulators. Small molecule inhibitors of IDH1 and/or IDH2 have shown great promise in early and mid-phase clinical trial testing. There are now multiple clinical trials studying the role of IDH1/2 inhibitors in newly diagnosed acute myeloid leukemia (AML) known to harbor an *IDH1* and/or *IDH2* mutation. Given the often proliferative pace of AML, this can optimally be accomplished with a rapid clinical assay that can provide genotyping results within 48-72 hours. We have developed an assay in collaboration with Integrated DNA Technologies (IDT) that utilizes a novel quantitative polymerase chain reaction approach with RNase H2-dependent PCR (rhPCR) to identify discrete canonical mutations in *IDH1* and *IDH2* in patient clinical samples.
Methods: Our laboratory has collaborated with IDT to create a laboratory-developed clinical test for identifying specific activating point mutations in *IDH1* and *IDH2* across a total of 6 common single nucleotide variants (SNVs). This assay relies on RNase H2-dependent release of a 3'-blocked primer to initiate PCR amplification in an allele-specific manner. Target-specific release of the blocker and subsequent allele-specific PCR with a mutant *Taq* DNA polymerase are highly sensitive to mismatch at the site of the SNV, resulting in a very high degree of SNV discrimination. Validation testing of this assay was conducted with 46 diagnostic patient tissue, blood, and bone marrow samples to establish assay specificity, accuracy, analytical sensitivity, and reproducibility. The fully optimized and validated assay has been clinically implemented for real-time prescreening of newly diagnosed AML patients for enrollment on to clinical trials 16-057 (Celgene-sponsored trial studying IDH1/2 inhibitors combined with hypomethylating agents) and 15-527 (Agios-sponsored trial studying IDH1/2 inhibitors in combination with induction chemotherapy), based on the presence of an *IDH1*/*IDH2* mutation.
Results: Validation testing using a variety of patient specimen types demonstrated analytic sensitivity as low as 1.6% to 0.4% with a high degree of technical reproducibility that ranged from 0.03% to 1.38%. In addition, results of rapid rhPCR testing across 18 samples with known *IDH1*/*IDH2* mutations were 100% concordant when compared to NGS testing. To date, rapid clinical rhPCR testing has been performed across 35 heme malignancy patients (16-057=11 pts; 15-257=24 pts). Mutations in *IDH1* have been identified in 11% of patients and mutations in *IDH2* have been demonstrated in 14% of patients, for an overall incidence of *IDH1/2* mutations of 25%, a rate consistent with published reports. From time of patient sample receipt into the clinical laboratory to final reporting to the clinician, testing was completed in as little as 3.5 h and up to 24 h (routine workdays).
Conclusion: An rhPCR-based assay coupled with a universal reporter system provides a rapid method for the detection of multiple *IDH1* or *IDH2* mutations in ~10% of the time it takes for traditional clinical NGS testing. This simple testing platform is easily integrated into a clinical testing workflow and is providing newly diagnosed AML patients access to cutting edge targeted agents as front-line therapy based on *IDH1/2* mutational status.

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Courtney A. Balliro, BS, RN, CDE, Medicine - Endocrine-Diabetes

Comparing the Patient Experience of Two Bionic Pancreas Systems

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Introduction: Automated glucose control is a rapidly progressing field of diabetes research, and many devices are approaching readiness to be marketed to consumers. As these systems evolve, the psychosocial experience of the user should be explored to provide input into future design and optimize educational plans for transitioning diabetes care to these devices. We have developed a closed-loop Bionic Pancreas system, which fully automates decision making for dosing and administration of insulin and/or glucagon in response to glucose level input from a continuous glucose monitor (CGM). The Bionic Pancreas can be used in a bihormonal (insulin and glucagon) or insulin only configuration. We compared the patient

experience of an insulin-only bionic pancreas (IOBP) as an alternative to the bihormonal (insulin and glucagon) bionic pancreas (BBP) using 8 different target glucose settings.
Methods: A 23 item survey modified from a longer instrument was administered to 24 participants with type 1 diabetes participating in an outpatient crossover home use study including 4 BBP arms (glucose targets of 100, 110, 115, and 130 mg/dl) and 4 IOBP arms (glucose targets of 110, 120, 130 and 145 mg/dl). These participants already used an insulin infusion pump to manage their diabetes care, but no exclusion criteria were set based on their current glycemic control. The survey, completed after each arm, assessed worry about blood sugars and confidence in the device. Answers were given a satisfaction score from 1(least) to 5 (most) and averaged to produce an overall score for each device. We compared both the patient experience of an IOBP as an alternative to the BBP, and the individual target glucose settings in each configuration.
Results: Participants were 38.6 ± 15.5 (20.8-77.6) years old, and presented with a 22.9 ± 12.9 year history of diabetes (5-54) and a Hemoglobin A1c of 7.3 ± 0.9% (6.1-9.3). The Bionic Pancreas demonstrated excellent glycemic control and minimal hypoglycemia in each configuration. Despite this, 70.8% (n=17) of subjects reported higher satisfaction for the BBP than the IOBP (p_s <.05). For the remainder of the subjects, there was no statistical difference between BBP and IOBP satisfaction scores. The BBP at a target of 110 mg/dl had the highest user satisfaction (4.35±0.25 of 5), that was not significantly different than a BBP at a target of 100 mg/dl (4.29±0.2 of 5, p=0.309). The 110 mg/dl BBP had significantly higher satisfaction when compared with all other BBP and IOBP configurations (p <0.000001-0.002). Subjects reported the largest difference when asked if the BP helped to prevent low blood sugars, reporting a mean score of 4.26 on the BBP compared to 2.53 on the IOBP. Subjects reported that they felt relaxed while wearing the BBP (4.48/5). On the BBP with a target of 110 mg/dl subjects reported the greatest peace of mind (4.58/5), the least amount of time spent worrying about their diabetes (4.32/5), and the strongest trust in the system (4.61/5). The system with the lowest overall satisfaction score was the IOBP with a target of 145 mg/dl (3.37±0.31 of 5).
Conclusion: This patient-centered data provides an enhanced understanding of subject diabetes related concerns and worries, as well as their confidence in the Bionic Pancreas. Participants were more comfortable with a BBP, regardless of glucose target, over the IOBP. All BBP systems were preferred over IOBP despite requiring daily reconstitution of lyophyilized glucagon. Development of stable, pumpable glucagon for use in the Bionic Pancreas could reduce this burden. This information helps research nurses to understand the diverse needs of the populations who may be using these devices and to guide teaching and device design to meet these needs. This will help nurses to anticipate subjects' perspectives and be prepared with specific support measures. It will allow nurses to provide comprehensive care and education to prospective and current research subjects in trials of a closed loop device, and to guide teaching and device design to meet the subjects' needs in the final configuration of the Bionic Pancreas. Future research should study the psychosocial impact of both systems over a longer period of time and help inform the final configuration of the Bionic Pancreas.

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Joshua A. Barocas, MD, Medicine - Infectious Diseases

Population level outcomes and cost-effectiveness of expanding guidance for age-based hepatitis C testing in the U.S.

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Introduction: Current guidance for hepatitis C virus (HCV) testing in the U.S. recommends routine, one-time testing among those born 1945-1965. Emerging data demonstrate that when this strategy is implemented, it misses opportunities to identify the substantial number of cases of HCV infection among those born after 1965. We used simulation modeling to investigate population-level outcomes and cost-effectiveness of expanding guidance for age-based HCV testing in the U.S.
Methods: We used an established Monte Carlo simulation of HCV testing and treatment (HEP-CE) to project the U.S. continuum of HCV-related care and estimated the cost-effectiveness of 4 strategies for HCV testing in the U.S.: 1) current standard of care, 2) routine testing for all persons aged ≥40, 3) aged ≥30 years, and 4) aged ≥18 years. All strategies assumed continued targeted testing of high-risk persons. We estimated HCV epidemiology using NHANES and cohort studies. We used MarketScan, a large claims-based dataset, to estimate current HCV testing rates and we calibrated those estimates to the positivity rate observed in two large commercial laboratory databases. Linkage and retention in HCV care varied by age and time-updated substance use behaviors. We modeled HCV treatment with sofosbuvir/velpatasvir and outcomes differed by fibrosis stage. Outcomes included cases of HCV infection identified, linked to care, and cured, liver-attributable mortality, quality-adjusted life years (QALYs), costs, and incremental cost-effectiveness ratios (ICERs).
Results: Current standard of care for testing resulted in 71% of cases being identified, 46% of HCV-infected persons were linked to care, and 44% of infected persons were cured over a lifetime. Expanded age-based testing strategies increased

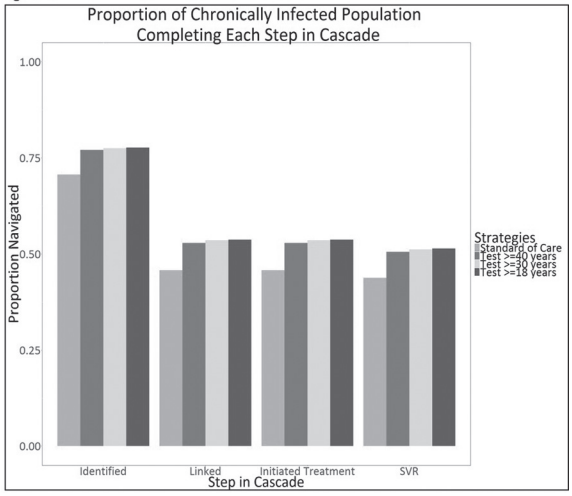
lifetime case identification rates by 6.4-7.0 percentage points and cure rates by 6.8-7.7 percentage points. Incremental lifetime costs of expanded testing ranged from $62-$75 and benefits of 0.0021-0.0026 QALYs. All strategies lay very close to the efficiency frontier, with testing all aged ≥18 years producing maximum benefit, with an ICER of $28,000/QALY compared to the next best strategy. Findings were robust in sensitivity analysis exploring variation in number needed to test to identify one case of HCV infection, linkage to care, cost, HCV-related utilities, and mortality.

Conclusion: HCV testing among all U.S. adults provides good economic value and is cost-effective. Our study is limited primarily by the limited availability of adequate national surveillance data for HCV infection and substance use disorder. Routine testing adults 18 years and older appears to be a reasonable national strategy to continue to combat the HCV epidemic and work toward elimination.

Table 1. Base case results and selected sensitivity analyses

Strategy	Incr Cost	Incr QALY	ICER ($/QALY)
Base Case			
Standard of Care	--	--	--
Test ≥40 years	$62.39	0.00214	Dominated
Test ≥30 years	$8.36	0.00037	Dominated
Test ≥18 years	$3.75	0.00014	$28,000
No utility benefit treating early stage			
Standard of Care	--	--	--
Test ≥40 years	$62.24	0.00206	Dominated
Test ≥30 years	$8.44	0.00034	$29,000
Test ≥18 years	$3.54	0.00011	$31,000
No change to cost in treated HCV			
Standard of Care	--	--	--
Test ≥40 years	$80.52	0.00214	Dominated
Test ≥30 years	$11.67	0.00037	$37,000
Test ≥18 years	$4.97	0.00013	$38,000
Inefficient screening scenario			
Standard of Care	--	--	--
Test ≥40 years	$74.30	0.00214	Dominated
Test ≥30 years	$10.75	0.00037	$34,000
Test ≥18 years	$6.02	0.00014	$44,000

Figure 1.



21

Devan D. Bartels, MD, MPH, Anesthesia, Critical Care and Pain Medicine

Estimating Pediatric General Anesthesia Exposure

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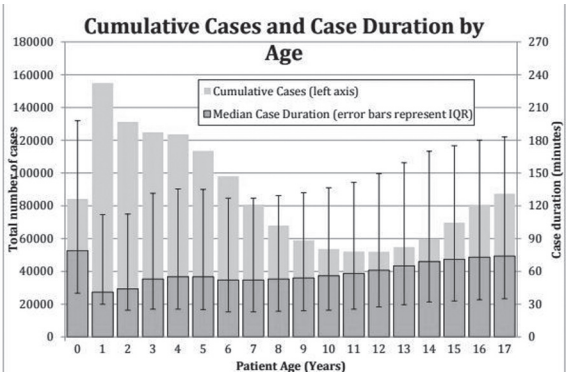
Introduction: Understanding the duration of pediatric general anesthesia exposure in contemporary practice is important for identifying groups at risk for long general anesthesia exposures and designing trials examining associations between general anesthesia exposure and neurodevelopmental outcomes.

Methods: We performed a retrospective cohort analysis to estimate pediatric general anesthesia exposure duration during 2010-2015 using the National Anesthesia Clinical Outcomes Registry (NACOR).

Results: A total of 1,548,021 pediatric general anesthetics were included. Median general anesthesia duration was 57 minutes (IQR 28-86) with 90th percentile 145 minutes. Children aged <1 year had the longest median exposure duration (79 minutes, IQR 39-119) with 90th percentile 210 minutes, and 13.7% of this very young cohort was exposed for greater than 3 hours. High ASA physical status and care at a university hospital were associated with longer general anesthesia exposure times.

Conclusion: While the vast majority of children undergoing general anesthesia are exposed for less than 3 hours, certain groups may be at increased risk for longer exposures. These findings may help guide the design of future trials aimed at understanding neurodevelopmental impact of prolonged general anesthesia exposure in these high-risk groups.



Cumulative case frequency and general anesthetic duration by age

22

Matthew Basilico, MD-PhD Candidate, Orthopedics

Initial Opioid Dosing Influences Long-Term Use: An Instrumental Variables Approach

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Introduction: The causal relationship between opioid dosing intensity and long-term opioid use is unknown.
Methods: We selected the setting of orthopedic trauma to minimize patient and physician selection behaviors, and to utilize first-year resident assignment to patients as an instrumental variable for opioid dosing intensity to estimate an average treatment effect. We performed a retrospective analysis of orthopaedic trauma patients who had not received a prescription for opioids in the 6 months before presentation at two level 1 trauma centers from 2002-2015. Post-operative prescription for each patient was predicted using a resident dosing leave-one-out estimator calculated from prescribing behavior on other patients. The effect of opioid prescribing on long-term opioid use was calculated using a maximum likelihood estimator with patient-level controls. Our primary outcome was long-term opioid use, defined as prescribing between three and six months after initial prescription.
Results: Our sample consisted of 2,097 patients. Resident prescribing varied widely; the resident dosing estimator was predictive of post-operative opioid prescription ($p < .001$, $R^2 = 0.24$). A one standard deviation increase in resident dosing propensity (166.4 morphine milligram equivalents (MME)) over the mean discharge dose (739.5 MME), increased the risk of long-term opiate use for the average patient from 24.42% to 32.28% (p=0.009, 95% confidence interval: 27.09% to 38.04%).
Conclusion: Wide variation exists in the initial opioid dose prescribed to post-operative, opiate-naïve orthopaedic trauma patients. We exploited this variation using an instrumental variables approach to quantitatively estimate the average effect of initial opioid dosing on long-term opioid use in a post-operative setting.

23

Sara V. Bates, MD, Pediatrics

Hypoxic-ischemic Encephalopathy: An Exploration of the MGHfC Neonatal Cohort

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Introduction: Hypoxic-ischemic encephalopathy (HIE) affects 1-3 per 1000 live births and is a leading cause of neurologic morbidity and mortality in childhood. The etiology of HIE is complex and is often multi-factorial with potential contributing factors from the fetus, placenta, maternal health, intrapartum events, and early resuscitative care. Identifying risk factors through a more detailed understanding of the clinical course and from quantitative imaging biomarkers may lead to improved prognostication paradigms that can aide medical providers and families in management decisions in this high-risk patient

population. Over the last decade, Therapeutic hypothermia (TH) has been shown to improve neurodevelopmental outcomes in infants with HIE and is considered standard therapy. The MGH Neonatal Intensive Care Unit (NICU) implemented the TH protocol in February 2009; however, the impact of this intervention on institutional HIE clinical and imaging data have not been rigorously evaluated to date.
Methods: A retrospective, IRB approved review identified clinical cases of HIE from 2003-2017. Cases with ICD-9/ICD-10 codes associated with perinatal brain injury or risk factors (e.g. low Apgar score or seizure) were included. Data were collected by expert chart review by three physicians. Data were entered and stored in the Partner's Research Electronic Data Capture (REDCap) system.
Results: Of the 144 cases of HIE reviewed to date 17% were born at less than 36 weeks of gestation, 59 % were born between 37-40 weeks of gestation, and 24% were born after 41 or more weeks of gestation. 39% of cases were born at MGH (inborn) and 61% were born at community hospitals (out-born) and transferred to the MGH NICU. 51% of the cohort was male and 49% were female. 53% of the infants were born to mothers who were less than 30 years of age and 18% were born to mothers ≥35 years old. Chorioamnionitis was documented in the medical record in 16% of cases and meconium was present in the amniotic fluid in 46% of cases. 56% of cases were delivered via cesarean section (MGH average annual c-section rate is close to 18%) and of the cesarean deliveries, 74% were identified as "emergency or stat." The 5 minute APGAR score was ≤5 in 70% of cases. The number of infants treated with TH at MGH since 2009 has ranged from 2-15/year for a total of 77 cases. TH inclusion criteria are: age ≤6hours, gestational age ≥35-36 weeks, moderate to severe encephalopathy on physical examination and/or seizures, history of an acute perinatal event, and moderately abnormal cord or infant blood gas within the first hour of life. In the TH group (cooled), 30 infants (39%) had clinical and/or electrographic seizures compared with 50 infants (76%) in a similar cohort prior to 2009.
Conclusion: The ability to accurately define the MGHfC cohort for HIE lays the foundation for more advanced statistical analyses and paves the way for validation studies. Our preliminary descriptive data is consistent with previous reports in the literature. In the future, we aim to continue to collect prospective data to evaluate associations between clinical factors and long-term neurodevelopmental outcomes in the MGH neonatal population with HIE. In addition, imaging data (MRI – T1, T2, DWI, spectroscopy) will be added from the Partners medical image repositories and scored by an expert panel of neuroradiologists. The combination of detailed clinical data (maternal background, delivery room experiences, infant's clinical course, outcomes, placenta pathology) and imaging quantification will make this one of the most comprehensive databases for studying perinatal brain injury in the country.

24

Benjamin Bearnot, Medicine - General Internal Medicine

Understanding Care for Patients with Opioid Use Disorder and Endocarditis: A Qualitative Study of Patients and Their Providers.

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Introduction: Opioid use disorder (OUD) is a public health emergency in the United States, and complications of OUD, including infectious complications like endocarditis, are accelerating. There is growing evidence that care for these patients is not comprehensive, and nuances of the arc of care, from hospitalization to post-acute care and then home, are understudied and poorly understood.
Methods: We conducted a qualitative study of patients with a diagnosis of at least mild OUD and a history of infective endocarditis (IE), with an index hospitalization at MGH. Patients were recruited from both ambulatory and inpatient settings. Health care providers (social workers, case managers, and nurses) caring for these patients were also identified and interviewed separately. After informed consent was obtained, we conducted in-depth, semi-structured interviews with a standard interview guide using domains that followed the arc of care from hospitalization to post-acute care and transitions home. Transcripts were analyzed independently by two readers per the principles of grounded theory using the constant comparative method. Participant enrollment will continue until thematic saturation is achieved.
Results: We have enrolled 10 participants to date, five patients and five providers. The five patient participants had a median age of 28 [IQR 26.5-42.5], with more than half identifying as white (n=4), female (n=3), and being unemployed or on disability at the time of index admission (n=3). Of five provider participants, four are social workers and one is a case manager. Patients and providers identified a number of important themes including stigma and biopsychosocial barriers to comprehensive care, cognitive sequelae of neurologic complications, and limited choices for post-acute care which compounds experiences of discontinuity in care for patients with OUD and IE. Representative quotes are listed below in Table 1.
Conclusion: Participants in this qualitative study on the care for patients with OUD and IE identified a number of barriers to comprehensive addiction and infection care in the acute and post-acute care settings. Our findings suggest that there is an

opportunity to improve the care we provide for these patients, and this study has identified a few key areas for care improvement and innovation, including integrated addiction care, equal access to post-acute care, and continuity of care for patients as they transition from hospital discharge to post-acute care and then home. Further research is needed to better understand the impact of our current care model for patients with OUD and IE on health outcomes.

Table 1: Identified Themes in the Care for Patients with OUD and IE.

Theme	Representative Quote
Patients	
Stigma towards OUD contributes to delays in care	"I don't think they looked at me as an individual. I think I was just a statistic, an addict, [a] paint-by-numbers kind of thing."
Poverty and homelessness	"I make hardly any money and pay child support. My insurance doesn't cover [the medications I need] so I kept putting it off and then boom, I got an infection [again]."
Sequelae of severe neurologic complications	"The infection broke off into my brain [...] damaged two of my heart valves, I had to learn to walk again, I lost all peripheral vision in my right eye. My brain was hemorrhaging, I was really, really bad."
Relapse and re-hospitalization	"I was in that hospital [...] stating that I would never use again, [but] the day I got out I had a needle in my arm and I was getting high again, wondering how the hell I got there and what happened."
Providers	
Limited choices for post-acute care	"[We're] asking people who have been doing well in a disease that we know can be treated [...] like cancer in long periods of remission, [but who] still aren't able to receive the standard level of care if they didn't have a substance use disorder."
Individualized treatment planning	"[discussing with patients] 'Let's open it all up. Let's just look at it. Where can we go with this? What do you need to know to make this decision? This is your decision. You're driving this.'"
Discontinuity of care	"Sometimes, we do all this great work [...] with a patient, then they go to a [post-acute care] facility and there is no one to continue it. So all that hard clinical work they did kind of falls away…"

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Jessica E. Becker, M.D., Psychiatry

Using a 78-year longitudinal study to examine the neuropsychiatric outcomes of childhood head trauma

J.E. Becker[1,2], M.D. Nevarez[1,2] and R.J. Waldinger[1,2]

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Introduction: Recent attention has been brought to the entity of chronic traumatic encephalopathy, a syndrome of progressive neurodegeneration after multiple head traumas, with clinical symptoms of behavioral changes, mood changes, and long-term cognitive impairment. Post-concussive syndrome is a related entity, in which neuropsychiatric symptoms can persist after a concussion for weeks or months. Much of the recent literature has focused on long-term pathophysiological and neuropsychiatric clinical changes in football players and veterans with frequent, severe head injury. Few studies, however, have longitudinally followed more generalizable cohorts to examine the long-term impact of early, mild head traumas on later-life neuropsychiatric outcomes in the population outside of professional sports or military, which has implication for early screening and management in the general population.
Methods: The study cohort is that of the ongoing, longitudinal Harvard Study of Adult Development. The cohort consists of 268 men born between 1915 and 1924 who were selected as sophomores at Harvard College for a study of male psychological health. While original selection criteria precluded the presence of physical or mental illness at intake, information about prior health experiences were collected for each study participant as part of a baseline assessment by physicians, psychologists, and anthropologists. The participants were followed every few years for the duration of their lives by questionnaire, in-person interview, and medical record collection. Later in life, 85 surviving members of the cohort underwent extensive neuropsychological testing. For the present study, data were abstracted from intake interviews with study participants at age 19 regarding childhood history of head trauma, including number of head injuries and presence and length of lost consciousness. Baseline data on concentration and memory, alcohol use, and perception of overall health were also abstracted. Outcomes among previously abstracted data include lifetime depression trajectories, impulsivity, and post-traumatic stress disorder symptoms after World War II. Among the subset for whom data were collected in late-life, neuropsychiatric testing results will also be examined in association with childhood head trauma.
Results: In total, there were 268 male college sophomores, ages 18-19, recruited for the study between the years 1939 and 1942. All study participants were white, and 50% received scholarship or worked to meet expenses during schooling. 260 of 268 served in World War II. Neuropsychiatric testing was collected for 85 (32%) of the study sample. Data collection has been ongoing for 78 years. Analyses will proceed from correlational and simple regression models to more complex modeling including potential mediators and moderators of outcomes to explore the relationships between childhood head trauma and lifetime depression trajectories, impulsivity, and post-traumatic stress disorder symptoms after World War II, as well as between childhood head trauma and later-life cognitive functioning.
Conclusion: Childhood head trauma data from a longitudinal study of human development could provide significant insight into the associations between early life head trauma and later life mental illness and cognitive functioning in a generalizable

cohort with more mild head trauma. Limitations of the data include subjective reporting by study subjects, as well as the study's homogeneous population. However, the long-term, longitudinal nature of the study can provide insights despite these limitations. The results may have implications for mental health interventions in childhood head trauma patients, which could ultimately lead to improved long-term clinical outcomes and cost savings.

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Kendra R. Becker, PhD, Psychiatry

Enhanced connectivity between caudate and default mode networks in anorexia nervosa is associated with increased drive for thinness and trait anxiety

K.R. Becker[8,2], E.A. Quattrocki[3,2], F. Plessow[4,5], C.J. Mancuso[4], A.M. Izquierdo[4], M. Slattery[4], K.A. Coniglio[1], C. Baskaran[4,6,7], E. Asanza[4], R.L. Pulumo[4], J.J. Thomas[8,2], T. Deckersbach[9,1,2], M. Misra[4,6,7], E.A. Lawson[4,5] and K.T. Eddy[8,2]

[1]Psychiatry, Massachusetts General Hospital, Reading, MA, USA, [2]Psychiatry, Harvard Medical School, Boston, MA, USA, [3]Psychiatry, McLean Hospital, Belmont, MA, USA, [4]Neuroendocrine Unit, Massachusetts General Hospital, Boston, MA, USA, [5]Medicine, Harvard Medical School, Boston, MA, USA, [6]Pediatric Endocrinology, Massachusetts General Hospital, Boston, MA, USA, [7]Pediatrics, Harvad Medical School, Boston, MA, USA, [8]Eating Disorder Clinical and Research Program, Massachusetts General Hospital, Boston, MA, USA and [9]Athinoula A. Martinos Center, Charlestown, MA, USA

Introduction: Resting-state fMRI has demonstrated aberrant processing in anorexia nervosa (AN), particularly in regions associated with self-referential thought (default mode network; DMN). Because resting state networks do not function independently, we explored inter-network connectivity between AN and healthy controls (HC) to further understand the pathophysiology underlying AN.
Methods: Thirty-four females (21 AN, 13 HC; age: mean±SD=19.4±1.7 years) underwent fMRI during rest. Independent component analysis extracted thirty resting-state networks (RSN) from the whole brain data. Eight networks were selected for further analysis. Permutation testing (50,000) on inter-network regularized partial correlation values established connectivity differences at the group level. Subjects also completed the Eating Disorder Inventory–Drive for Thinness (EDI-DFT) and State Trait Anxiety Inventory (STAI).
Results: Compared to HC, AN exhibited increased temporal coherence between the caudate network and the DMN (p=.03). Across groups, higher EDI-DFT and STAI scores (r's≥.53, p's≤.001) correlated with this enhanced connectivity.
Conclusion: Increased connectivity of the DMN and caudate RSN in AN indicates a pairing of increased self-focus with goal-directed behavior. The association between DMN and caudate RSN inter-network connectivity strength with drive for thinness and trait anxiety suggests that self-referential weight/shape goals relate to mechanisms of action execution in AN.

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Abigail Belser, BA, Psychiatry

Diagnostic Validity of a DSM-based Autism Spectrum Disorder Symptom Checklist Compared to the Autism Diagnostic Observation Schedule

A. Belser, M. Fitzgerald, M. Galdo, R. Fried, B. Hoskova, M. de Leon, J. Biederman and G. Joshi

Pediatric Psychopharmacology, Massachusetts General Hospital, Boston, MA, USA

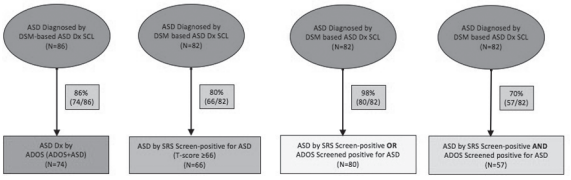
Introduction: Diagnosing autism spectrum disorder (ASD) can be a lengthy and expensive process. There is a need for a simplified and accurate assessment to aid in the diagnosis of ASD. This study assessed the validity of a DSM-based diagnostic symptom checklist for the assessment of ASD in psychiatrically referred populations.
Methods: Assessment data from children and adults aged 8-57 with a clinical diagnosis of ASD, was collected to assess the validity of a DSM-based autism spectrum disorder symptom checklist (ASD-SCL). The assessments included the Autism Diagnostic Observation Schedule (ADOS), Social Responsiveness Scale (SRS), as well as the DSM-based MGH ASD-SCL. We assessed the agreement of an expert clinician administered MGH ASD-SCL with the ADOS and SRS, both reliable measures to aid in diagnosing ASD.
Results: 86 subjects were assessed with the MGH ASD-SCL, ADOS, and SRS. There is a strong agreement between the MGH ASD-SCL and the ADOS [86%], as well as the MGH ASD-SCL and the SRS [80%]. 98% of subjects that met criteria for ASD on the MGH ASD-SCL also met on either the ADOS or SRS.
Conclusion: A DSM-based ASD-SCL could serve as a useful diagnostic aid in assessment of ASD in psychiatrically referred populations. Further assessment of the psychometric properties is warranted.

Demographics

	ASD
Total Participants	86
Age	
Mean (Range)	21.1±9.6 (8-57)
Adults (≥18)	50 (58)
Youth (<18)	37 (43)
Adolescents (13-17)	27 (31)
Pre-adolescents (≤12)	10 (11)
Gender: Male	67 (79)
IQ (Full Scale)	109±16 (75-144)
Clinical Characteristics	
DSM-IV ASD Diagnostic Subtypes (n=33)	
Autistic Disorder	23 (70)
Asperger	7 (21)
PDD-NOS	3 (9)
DSM-V ASD Diagnostic Subtypes (n=53)	
Autism Spectrum Disorder	53 (100)

Values expressed as N (%) or Mean +/- Standard Deviation

Figure I. ASD-SCL Diagnostic Correspondence with ADOS and SRS



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Abhiram R. Bhashyam, MD, Orthopedics

An analysis of initial post-operative opioid prescribing patterns in orthopaedic trauma and a technique to determine prescribing guidelines

A.R. Bhashyam[1], M. Basilico[1], M. Harris[2] and M. Heng[1]

[1]Orthopaedic Surgery, MGH, Boston, MA, USA and [2]Orthopaedic Surgery, BWH, Boston, MA, USA

Introduction: Prescription opioids are the initial mainstay of post-operative pain management in orthopaedic trauma in North America, but there is limited data to guide post-operative prescribing. We examined the variation in post-operative opiate prescribing patterns at discharge within two American College of Surgeons level I trauma centers for opiate-naïve patients who had sustained a fracture. We aimed to create a prescribing guideline by AO/OTA fracture classification based on an analysis of our institutional experience and using prior evidence that 225 morphine milligram equivalents (MME) is an appropriate maximum prescribing dose for the majority of patients with operatively treated distal radius fractures.

Methods: We performed a retrospective analysis of post-operative orthopaedic trauma patients from 2002-2015 who were treated at one of two trauma centers. Principle to their inclusion in this cohort was that they were defined as opiate-naïve (they had not received a prescription for opioids in the 6 months prior to presentation). We analyzed the quantity of initial opioids prescribed in MME by the AO/OTA fracture classification. We controlled for patient age, gender, and comorbidity using multivariate linear regression.

Results: Our sample consisted of 6879 patients. We found significant variation in initial opioid prescribing by AO/OTA classification ($p<0.001$). Compared to patients with distal radius fractures, patients with operative pelvic/acetabulum (coefficient 255-295 MME, $p<0.001$), femur (coefficient 238-323 MME, $p<0.001$), and tibia (coefficient 136-242 MME, $p<0.001$) fractures were prescribed significantly more opioids at the time of discharge. Among patients who sustained non-diaphyseal long bone fractures, there was no difference in the quantity of opiates prescribed between extra-articular and intra-articular fractures. Similarly, for patients with operatively treated diaphyseal fractures, there was no difference in prescribed opioids by shaft fracture morphology.

Conclusion: We demonstrate significant variation in initial post-operative opioid prescribing to opiate-naïve orthopaedic trauma patients by fracture classification. We propose a method and provide an example (Table 1) of how to create a post-operative prescribing guideline using the AO/OTA fracture classification.

Fracture location	MME on discharge †	Additional MME (over 225 MME)	Number of additional 5 mg oxycodone tablets*	Example of initial prescription for opioids on discharge
Radius/ulna - Distal	*225 MME base case* [16]	---	---	30 tablets of 5 mg oxycodone
Ankle/Malleolar	279	54	7	35 tablets of 5 mg oxycodone
Humerus - Proximal	281	56	7	35 tablets of 5 mg oxycodone
Radius/ulna - Proximal	293	68	9	40 tablets of 5 mg oxycodone
Humerus-Diaphyseal	323	98	13	40 tablets of 5 mg oxycodone
Humerus - Distal	329	104	14	45 tablets of 5 mg oxycodone
Tibia - Proximal	379	154	21	50 tablets of 5 mg oxycodone
Radius/ulna - Diaphyseal	434	209	28	60 tablets of 5 mg oxycodone
Femur - Proximal	463	238	32	60 tablets of 5 mg oxycodone
Tibia - Diaphyseal	467	242	32	60 tablets of 5 mg oxycodone
Tibia - Distal	480	255	34	65 tablets of 5 mg oxycodone
Pelvic ring	480	255	34	65 tablets of 5 mg oxycodone
Femur - Distal	480	255	34	65 tablets of 5 mg oxycodone
Acetabulum	520	295	39	70 tablets of 5 mg oxycodone
Femur - Shaft	553	328	44	75 tablets of 5 mg oxycodone

MME = morphine milligram equivalents; †From Table 2 regression results;
*Calculation of tablets = (Additional MME) / (mg/pill) (conversion factor)[10]

Table 1: Potential Initial Opioid Prescribing Guideline and Example Calculation

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Jasmine M. Blake, MSPH, Pediatrics

Predictors of Post-Discharge Outcomes and Care Seeking Behaviors among Children with Acute Infectious Illness in Southwestern Uganda

J.M. Blake[1,2], M.O. Wiens[4], A. Gellman-Chomsky[1] and P.P. Moschovis[3,1]

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Introduction: Substantial progress has been made in the global reduction of under-5 mortality rates (U5MR) among children. Despite the progress, rates continue to be elevated in many low and middle income countries, particularly in Sub-Saharan Africa. Acute infectious illnesses account for the majority of under-5 childhood deaths in Sub-Saharan Africa. Existing research has focused on prevention and treatment of such illnesses, but little research has focused on children who have survived episodes of acute infectious illness. Our previous work demonstrated that post-discharge and in-hospital mortality rates among children with acute infectious illness are similar, yet little is known about the predictors of health outcomes and care-seeking behaviors following hospital discharge. This study aims to understand predictors of post-discharge outcomes and care-seeking behaviors among children in Uganda.

Methods: Children 6 months to 5 years of age with a proven or suspected acute infectious illness who presented to Mbarra Regional Referral Hospital or Holy Innocents Children's Hospital were enrolled in this prospective cohort study. Following discharge from the hospital, children received telephone and/or in person follow-up visits at 2, 4, and 6 months. During follow-up, information concerning mortality, readmission, recurrence of illness, and care-seeking behaviors were asked. Utilizing this data, geospatial analysis was conducted to determine nearest distance to health facilities and statistically significant clustering of events. Results of the geospatial analysis were included in both univariate and multivariate logistic regression models to determine the geographical, clinical, and sociodemographic predictors of post-discharge outcomes and care-seeking behaviors.

Results: Of 1,307 children enrolled, 1,242 were discharged alive of whom 68 (5.5%) died and 206 (16.6%) were readmitted. Geospatial analysis revealed statistically significant clustering of post-discharge mortality and care-seeking. Multivariate analysis determined that 1 kilometer increases in distance from the nearest level three health facility increased the odds of mortality by 8% (OR 1.08 95% CI 0.99-1.17) (Fig 1). Despite the average nearest health facility being 2.32 kilometers away, 1 kilometer increases in distance from the nearest health facility increased the odds of mortality by 9% (OR 1.09 95% CI 0.93-1.27) though results were not statistically significant. Analysis also indicated that previous hospitalization within 7 days and within 7-30 days increased the odds of post-discharge readmission as compared to no hospitalization (OR 3.08 95% CI 1.58-6.02 and OR 1.87 95% CI 1.04-3.38, respectively). Decreased odds of post-discharge readmission were associated with lengths of stay of 5-10 days and >10 days as compared to <3 days (OR 0.55 95% CI 0.32-0.94 and OR 0.40 95% CI 0.17-0.95, respectively) as well as for every 1 kilometer increase in distance from the nearest health facility (OR 0.91 95% CI 0.84-0.99) (Fig 2). Predictors of care-seeking included age >24 months (OR 2.80 95% CI 1.01-5.61) and 1 kilometer increases in distance from the nearest health facility (OR1.23 95% CI 1.01-1.50). Children described as very sick post-discharge were less likely to seek care than those who were described as being a little sick post-discharge (OR 0.11 95% CI 0.04-0.32).

Conclusion: Several predictors of post-discharge outcomes and care-seeking behavior were determined, most notably, the effect of distance from a healthy facility on post-discharge death. Although distance was associated with each outcome, the relationship between distance and level of health facility was most striking for post-discharge mortality, suggesting that level of health facility and not just distance to any type of health facility contributes to post-discharge mortality. These results provide insight for the development of targeted post-discharge community-based interventions and health system restructuring to reduce U5MR and morbidity in Sub-Saharan Africa.

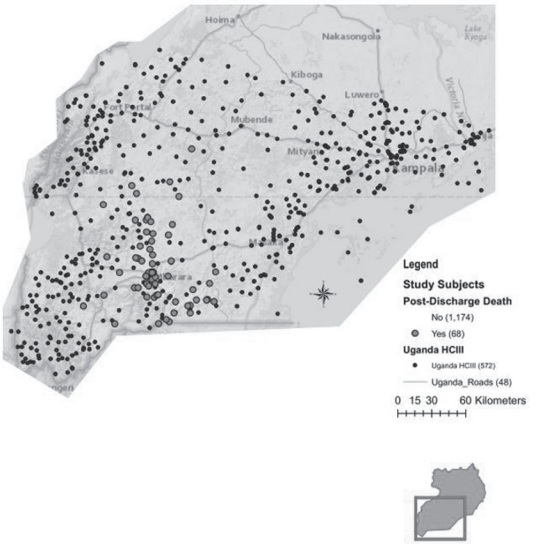

Figure 1 Post-Discharge Deaths in Proximity to Level III Health Facilities

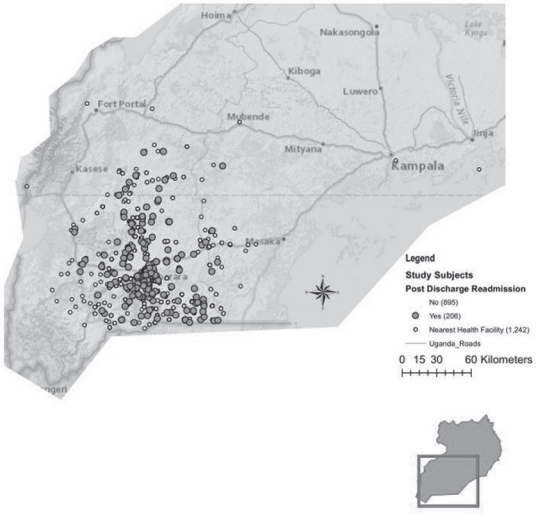

Figure 2 Post-Discharge Readmission and Proximity to Nearest Health Facilities

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Daniel M. Blumenthal, MD, MBA, Medicine - Cardiology

Phone-Based Assessment of Angina Prevalence and Severity Among Primary Care Patients with Coronary Artery Disease: Interim Results and Observations

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Introduction: The presence and severity of angina are strong predictors of mortality due to coronary artery disease (CAD), morbidity, reduced quality of life, and health care spending. To our knowledge, no previous work has characterized angina prevalence among primary care patients with CAD. Also, insurers are increasingly requiring angina assessment as a prerequisite for payment for CAD treatments. Within Partners Healthcare, administration of validated patient reported outcomes measures (PROM) to assess angina, including the Seattle Angina Questionnaire-7 ("SAQ-7"), during clinic appointments has been limited by response rates < 20%. We designed and implemented a quality improvement project to assess the feasibility and value of phone-based SAQ-7 administration to CAD patients who receive primary care through the Massachusetts general Hospital's (MGH) primary care clinics and affiliated health centers.

Methods: All patients with CAD who were at least 30 years old and received primary care through one of 15 MGH primary care clinics and health centers were eligible to participate. Patients were excluded if they were deceased, or deemed unable to complete a survey (due to dementia, hearing impairment, or a language barrier). CAD patients were identified using the MGH Primary Care Practice Based Research Network ("PBRN"), which contains 161,000 patients who receive primary care through the MGH primary care network. A validated, electronic algorithm with billing code and other information from electronic health records was used to identify 10,000 patients in the PBRN with CAD as of June 30, 2016. Compared to manual chart review (e.g. the "gold standard"), the search algorithm identified CAD patients with a sensitivity and specificity of 90% and 90%, respectively. The SAQ-7, a validated seven question PRO instrument for assessing angina frequency, severity, and health impact, was administered by eight Massachusetts General Physicians Organization Population Health Coordinators (PHCs), each of whom was affiliated with ≥ one MGH primary care clinic. Seven PHCs administered surveys in English; one Spanish-speaking PHC administered a validated Spanish translation of the SAQ-7 to eligible Spanish-speaking patients. PHCs performed ≥ one follow-up call for patients who did not answer their phone, or who did not return a voice message from a PHC within 24 hours. Survey administration was overseen by the MGPO as part of a quality improvement project and therefore exempted from institutional review board (IRB) approval. Survey completion implied consent. This analysis

includes data collected between February-May, 2017. PHCs recorded survey responses in a patient's EHR immediately following survey administration. PHCs were asked to separately document the call date and length, the patient's survey completion status and relevant notes, including plans for follow-up calls, in the excel file containing their patient lists. Key measures assessed in this interim analysis include numbers of patients contacted, survey response rates, and reasons for survey non-completion. These measures were determined for the entire cohort, by PHC, clinic, patient sex, and primary language. SAQ-7 responses were not analyzed at this juncture. Analyses were performed using Microsoft Excel. The data analysis portion of this project was approved by the MGH IRB (protocol #: 2016P002476/PHS).

Results: PHCs performed chart reviews for and/or contacted 922 patients (9.2% of CAD sample); 53 patients (5.7% of reviewed sample) were determined to be deceased and were excluded (**Table 1)**. Of the remaining 869 patients, 274 (31%) completed the survey. Survey completers were slightly younger than survey non-completers (mean age: 74.4 years vs. 75.8 years), and survey completion rates were higher among women than men (34.3% vs. 30.1%). In addition, survey completion rates among patients surveyed in Spanish were higher than among English-speaking patients (40.3% vs. 31.0%). Among the 593 non-responders, 436 patients (73.5%) did not answer their phone or respond to voice messages left by PHCs; 95 (16.0%) were unable to complete the survey; and 62 (10.4%) refused to participate. Survey completion rates ranged from 18.6%–40.8% across PHCs, and 11.7%–42.1% across the fourteen clinics with ≥ one survey attempt.

Conclusion: Phone-based administration of the SAQ-7 to English and Spanish-speaking outpatients with CAD is feasible, and yields response rates that compare favorably with SAQ-7 administration in outpatient clinics. Further work is needed to assess the value of this mechanism of administering PROMs and to determine if the mode of PROMs administration influences patients' responses.

Table 1: Patient Characteristics By Survey Completion Status

	Completed Survey (N= 274)	Did not Complete Survey[1] (N=593)
Mean age—years (SD)	74.4 (10.8)	75.8 (11.9)
Gender—N (%)		
Male	171 (30.2)	396 (69.8)
Female	103 (34.3)	197 (65.7)
Language—N (%)		
English	243 (31.03)	540 (68.97)
Spanish	29 (40.3)	43 (59.7)
Other	2 (16.67)	10 (83.33)
Population Health Coordinator (PHC)—N (% of patients contacted by PHC)		
PHC #1	49 (33.5)	97 (66.5)
PHC #2	12 (30.0)	28 (70.0)
PHC #3	75 (40.3)	111 (59.7)
PHC #4	22 (18.6)	96 (81.4)
PHC #5	29 (33.3)	58 (66.7)
PHC #6	34 (24.3)	106 (75.7)
PHC #7	24 (30.4)	55 (69.6)
PHC #8	29 (40.8)	42 (59.2)
MGH Primary Care Clinics—N (% patients contacted by clinic)		
Bulfinch Medical Group	20 (28.6)	50 (71.4)
Internal Medicine Associates	12 (30.0)	28 (70.0)
Mass General Medical Group	14 (20.0)	56 (80.0)
MGH Back Bay	25 (37.9)	41 (62.1)
MGH Beacon Hill	17 (29.8)	40 (70.2)
MGH Charlestown Adult	17 (29.3)	41 (70.7)
MGH Chelsea Adult Medicine	48 (42.1)	66 (57.9)
MGH Downtown	15 (34.9)	29 (65.1)
MGH Everett Family Care	15 (25.9)	43 (74.1)
MGH Revere Broadway	17 (37.8)	28 (62.2)
MGH Revere Healthcare Center	7 (11.7)	53 (88.3)
MGH Senior Health	10 (22.7)	34 (77.3)
North End Waterfront Health	–	–
Primary Care Associates	50 (41.67)	70 (58.33)
Women's Health Associates	7 (33.3)	14 (66.7)
Reasons for Survey Non-Completion—N (% all non-completed surveys)[1]		
Refused	–	62 (10.5)
Unable to complete[2]	–	95 (16.0)
Other reasons[3]	–	436 (73.5)

Notes: [1]Patients targeted by population health coordinator for survey completion, but who did not complete a survey; does not include deceased patients. [2] Unable to complete due to dementia, hearing impairment, language barrier, or wrong phone number. PHCs determined patients' inability to complete surveys. [3] Other reasons defined as: patients who did not answer their phone, didn't respond to messages left by PHCs by voice mail or with household member, or for whom contact information was incorrect.

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Kimberly G. Blumenthal, MD, MSc, Medicine - Allergy/Immunology/Rheumatology

Tackling Inpatient Penicillin Allergies: Assessing Tools for Antimicrobial Stewardship

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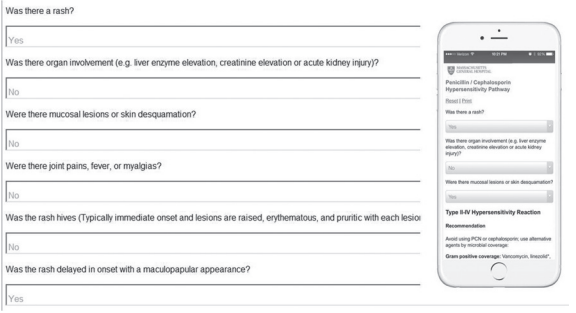
Introduction: Reported penicillin allergy rarely reflects penicillin intolerance. Failure to address inpatient penicillin allergies results in more broad-spectrum antibiotic use, treatment failures, and adverse drug events. We aimed to determine the optimal approach to penicillin allergies among medical inpatients.

Methods: We evaluated internal medicine inpatients reporting penicillin allergy in three periods: (1) standard of care (SOC), (2) penicillin skin testing (ST), and (3) computerized guideline application with decision support (APP, Figure 1). The primary outcome was use of a penicillin or cephalosporin, comparing interventions to SOC using multivariable logistic regression.

Results: There were 625 patients: SOC 148, ST 278, and APP 199 (Figure 2). Of 278 ST patients, 179 (64%) were skin test eligible; 43 (24%) received testing and none were allergic. In the APP period, there were 292 unique website views; 112 users (38%) completed clinical decision support. While ST period patients did not have an increased odds of penicillin or cephalosporin use overall (aOR 1.3 [95% CI 0.8, 2.0]), we observed a significant increased odds of penicillin or cephalosporin use overall in the APP period (aOR 1.8 [95% CI 1.1, 2.9]), and in a per protocol analysis of the skin tested subset (aOR 5.6 [95% CI 2.5, 12.4]).

Conclusion: Both the computerized guideline with decision support and penicillin skin testing – when completed – increased use of penicillin and cephalosporin antibiotics among inpatients reporting penicillin allergy. While the skin tested subset showed an almost 6-fold impact, the computerized guideline significantly increased penicillin or cephalosporin use overall nearly 2-fold and was readily implemented.

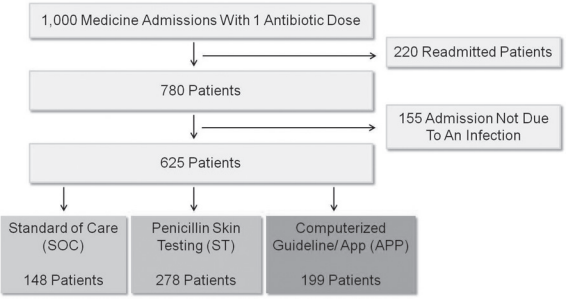


The computerized guideline/website contained optional clinical decision support for taking a drug allergy history. After answering questions from the patient history, the app would group immunologic reactions into one of three categories:

(1) Type II-IV hypersensitivity reaction, avoidance of beta-lactams generally recommended

(2) Type I IgE-mediated hypersensitivity reaction, 3rd/4th/5th generation cephalosporins can be used by test dose directly; to use of 1st/2nd generation cephalosporins or penicillins, penicillin skin testing (academic hospitals) or desensitization or Allergy/Immunology follow up (community hospitals) was recommended.

(3) Mild hypersensitivity reaction including electronic health record discrepancies and benign morbilliform rashes, 3rd/4th/5th generation cephalosporins can be used by full dose and 1st/2nd generation cephalosporins and penicillins can be used by test dose.



This flow chart demonstrates patient cohort identification. The care redesign team was notified prospectively if patients met initial criteria, including (1) internal medicine inpatient, (2) reported penicillin allergy, and (3) prescribed one or more antibiotic doses. From this cohort, we excluded readmissions and patients whose admission was not for treatment of an infection. Of 625 patients meeting these criteria, 148 were admitted in the standard of care period, 278 were admitted in the penicillin skin testing period, and 199 were admitted in the computerized guideline period.

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Pietro Bortoletto, MD, OB/GYN

The Effect of Clomiphene Citrate (CC) Dose and Initiation Day on Endometrial Thickness (ET) in Women Undergoing Clomiphene Citrate/Intrauterine Insemination (CC/IUI) Cycles

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Introduction: To evaluate whether CC dose and initiation day affects ET in patients undergoing CC/IUI cycles we designed a retrospective cohort study at a large academic fertility center.
Methods: Data from 2453 CC/IUI cycles (1051 women) that took place between 12/2003 to 12/2015 were reviewed. Patients underwent CC/IUI ultrasound monitored and hCG-triggered cycles with an individualized 5-day course of CC at doses ranging from 25, 50, 100 or 150 mg starting on either cycle days 2, 3, 4, 5, or 6. A mixed random and fixed effects general linear model was conducted with a backward elimination algorithm ($p<0.01$ cutoff) where ET was the dependent variable and both CC dose and initiation day were the primary fixed effect predictors. Age, body mass index (BMI) and day-3 FSH were included as covariates.
Results: Mean (SD) age, BMI, day-3 FSH, and ET at first cycle were: 33.5 (4.3) years, 24.5 (4.7) Kg/m^2, 7.1 (2.8) IU/L, and 7.0 (2.1) mm, respectively. Both BMI and treatment attempt number (1st vs. repeat attempt after prior conception cycle) correlated positively with ET ($p<0.0001$). Significant interactions between i) CC dose and initiation day ($p=0.003$), and ii) CC dose and day-3 FSH ($p=0.01$) were noted. Overall, higher CC doses initiated at later cycle days were associated with a thinner ET. Similarly, higher CC doses in patients with higher day-3 FSH levels (FSH: 10 IU/L) were also associated with a thinner ET. Specifically, in all patients with later CC cycle starts (day-4 or day-5), the endometrium became thinner as the CC dose increased, irrespective of the patient's day-3 FSH level. However, in patients with lower FSH levels (FSH: 5 or 7 IU/L), if CC was started earlier (day-2 or day-3) then the increase in the dose did not negatively affect the ET.
Conclusion: Our results suggest that effects of CC on ET vary depending on dose, initiation day and day-3 FSH levels. When using higher doses of CC (100 or 150 mg), earlier cycle start (day-2 or day-3) might attenuate CC negative's effect on ET irrespective of day-FSH levels.

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Ryan Bottary, BS, Psychiatry

Daytime Sleep, SWS Spindle Activity and Acute Emotion Regulation in Social Anxiety Disorder

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Introduction: Sleep promotes emotional memory consolidation. Yet, sleep's impact on acute emotion regulation remains largely unknown. We explored daytime sleep's impact on affect, anxiety, and sleepiness following an experimental stressor in individuals with Social Anxiety Disorder (SAD; Experiment-1) and healthy controls (HC; Experiment-2).
Methods: Twenty-five SAD and 36 HC subjects completed one (HC) or two (SAD) experimental stressor sessions (SAD: social exposure; HC: viewing highly aversive photographs) followed by a 120-minute PSG-recorded nap (Nap-Condition) or wake (Wake-Condition) opportunity. Positive and Negative Affect Schedule (PANAS+/-), Spielberger State-Trait Anxiety Inventory-State (STAI-S), and Stanford Sleepiness Scale (SSS) were completed pre- and post-session. For SAD, canonical (13.5Hz), fast (15Hz), and slow (11Hz), spindles were detected bilaterally in artifact-free EEG using co-author S.P.'s open source wavelet analysis program (http://zzz.bwh.harvard.edu). Spindle amplitude, density and duration was calculated for detected spindles.
Results: *Experiment 1*: Two (Condition: Nap/Wake) x 2 (Session: 1/2) x 2 (Time-Point: Pre-Session/Post-Session) ANOVAs, performed independently for SSS, PANAS+, PANAS-, and STAI-S scores, revealed main effects of Time-Point for SSS, (Post>Pre; $F(1,24)=12.67, p=0.002$), PANAS+, (Post<Pre; $F(1,24)=47.03, p=0.0001$), PANAS-, (Post<Pre; $F(1,24)=45.28, p=0.0001$), and STAI-S, (Post<Pre; $F(1,24)=15.20$, $p=0.0007$), and Session for PANAS+, (1>2; $F(1,24)=7.17, p=0.013$, and PANAS-, $F(1,24)=7.27, p=0.013$, Time-Point x Condition interactions for PANAS+, $F(1,24)=9.29, p=0.006$, and PANAS-, $F(1,24)=5.42$, $p=0.029$, and a Session x Condition interaction for PANAS+, $F(1,24)=9.53, p=0.005$. Increased post-nap sleepiness correlated with sleep-onset latency ($r=0.69, p=0.03$) and fast N3 sleep spindle density ($r=0.861, p=0.013$) and duration ($r=0.808, p=0.028$), which also correlated with increased post-nap negative affect ($r=0.848, p=0.016$). Finally, increased post-nap positive affect correlated with slow N3 spindle duration ($r=0.756, p=0.049$). *Experiment 2:* Two (Condition: Nap/Wake) x 2 (Time-Point: Pre-Session/Post-Session) ANOVAs, performed independently for PANAS+, PANAS-, and SSS, revealed a main effect of Time-Point for PANAS+,

(Post>Pre; F(1,34)=6.72,p=0.01), PANAS-, (Post<Pre; F(1,34)=21.97,p<0.001), and SSS, (Post<Pre; F(1,34)=7.68,p=0.009), suggesting that both napping and wake increased positive affect, decreased negative affect and reduced sleepiness.
Conclusion: Napping dampened positive and negative affect and increased sleepiness in SAD but not HC. For SAD, fast and slow N3 spindle activity differentially impacted emotion regulation and sleepiness. These differing patterns suggest a possible deficiency in sleep-dependent emotion-regulatory processes in anxiety disorders.

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Ellen B. Braaten, Ph. D., Psychiatry

Impaired processing speed: an under-studied phenomenon across neuropsychiatric disorders in youth

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Introduction: Impaired speed of information processing or **"**processing speed; (PS)" is associated with difficulties in academic and adaptive functioning. PS as a cognitive construct has been examined extensively in attention deficit hyperactivity disorder (ADHD), but to a more limited degree in other neuropsychiatric conditions. We aimed to extend the literature by examining PS across a range of conditions in a cohort of clinically referred youth. Our goals were to elucidate the role of neuropsychiatric diagnosis, psychiatric comorbidity and transdiagnostic psychopathology traits in the prediction of impaired PS.
Methods: Data were from 775 youth, ages 6-21, consecutively referred for neuropsychiatric evaluation and enrolled in the Longitudinal Study of Genetic Influences on Cognition (LOGIC). Processing speed was calculated using measures from the Wechsler intelligence scales, which are population-normed and have robust psychometric properties. Data were analyzed using mixed modeling, ANOVA and logistic regression while controlling for age, sex and use of psychotropic medication.
Results: In this clinical cohort, PS was significantly more impaired than either of the other two major domains of functioning on the Wechsler Intelligence Scales, including working memory ($M_{difference}$ = -1.3, p=.03) and general cognitive ability ($M_{difference}$ = -9.0, p<.001). Although not the case for youth with anxiety disorders, youth with psychosis, autism spectrum disorder (ASD), mood disorders and ADHD all performed below national norms on PS. Controlling for comorbidity, the presence of psychosis (OR=3.5), ASD (OR=1.8) and ADHD (OR=1.5) increased the risk of having slow processing speed (PSI<85). Among dimensional measures of the psychopathological conditions we examined, only inattention (OR=1.4) was a significant predictor of risk for impaired PS across disorders.
Conclusion: Impaired PS is relevant to neuropsychiatric conditions beyond ADHD. Our data raise the possibility that the dimensional construct of inattention accounts for impaired PS across disorders.

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Katie Brandt, MM, Neurology

Harmonizing Together: Speech-language and Music Therapy and Support for Patients and Partners with PPA

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Introduction: Participation in a support group can help patients and their partners to realize there are other people who are experiencing similar problems to theirs. Specific support groups exist for Alzheimer's Disease, aphasia from a stroke, and traumatic brain injury, but there are limited group opportunities for patients and families suffering from Primary Progressive Aphasia (PPA). The needs of the patient and family with PPA are unique. Due to a paucity of support groups geared to PPA, we sought to develop and evaluate a multidisciplinary group targeting their specific needs. The goals of this group are to: Provide interdisciplinary therapy and support to patients with early stage PPA and their caregivers Provide functional communication strategies Decrease isolation for patients and caregivers Support caregiver resilience Educate about PPA and current research and resources
Methods: Eight weekly 90 minute sessions of 45 minutes of speech-language therapy (mostly patients only) and caregiver support and 45 minutes of group music therapy Care partners and patients given separate pre- and post-group surveys with Likert scale and open-ended questions Data was compiled individually across questionnaire items on the pre- and post- group surveys Averages were calculated across individual questions to obtain a numerical indicator for each survey question The numerical difference between pre- and post- group survey questions were calculated to analyze the change in response on

questionnaire items status post PPA group Bar graphs were created to analyze the difference of responses after group The pre- and post- group data were then analyzed for significant change using multiple paired t-Tests

Results: Eight dyads participated. Analysis of pre- and post-group surveys identified 2 of 65 items that changed ($p<0.05$), including caregivers having more time for themselves and patients having more feelings of guilt. Other items showed trend level changes ($p<0.1$), including an improvement in caregiver health. Examples of observations of possible relevance include an increase in: strategies to compensate for language impairment, social participation of patients, and caregiver fear regarding the future. Error bars on the bar graphs indicate the standard error of the mean.

Conclusion: The reports of improvement in caregiver health, social participation of patients, and functional communication are in line with the group's focus and goals. In contrast, more comprehensive knowledge of the disease process may have led patients and caregivers to experience greater feelings of guilt and fear. Our qualitative observations and reports from participants indicated that the most beneficial parts of the group were raising patients' confidence in communication and allowing both patients and families suffering from PPA to connect with one another. Patient confidence in communication ability was also noted when comparing results on perceived decline in patient communication; patients did not see a decline whereas caregivers did. For future groups, including quality of life measures before and after participation and using a control group may show additional benefits of connecting with the community. Future evaluation tools may focus more on the impact of connecting with the PPA community and building new relationships with other patients and caregivers.

Do you feel the time spent being a care partner causes you to have less time for yourself?

Care Partner Response BEFORE	Care Partner Response AFTER
2	1.5

Scale 0 Never 1 Rarely 2 Sometimes 3 Quite Frequently 4 Nearly Always

Do you feel guilty about the time and effort your care partner spends on you?

Patient Response BEFORE	Patient Response AFTER
2.25	3.25

Scale 1 Never 2 Hardly Ever 3 Sometimes 4 A lot of the time

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Kathleen M. Breda, MSN, BSN, BBA, AGACNP-BC, Nursing

An Evaluation of Interdisciplinary Neurosurgical Clinician Perspectives on Post-Operative Cranial Dressing Strategies

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Introduction: Clinicians describe different practice experiences with post-operative cranial dressing strategies. Postoperative wound management is the responsibility of the entire neurosurgical team, including ICU nurses. Research on cranial dressing strategies is limited, thus, evidence to support a practice change is lacking. Eliciting perspectives from neurosurgical clinicians from diverse practice backgrounds may establish practice-based evidence to inform clinical practice for cranial incisions. This study explored, among interdisciplinary neurosurgical clinicians, experiences with current cranial dressing strategies, including dressing effectiveness, stability, and removal.

Methods: This qualitative descriptive study included a convenience sample of neuroscience ICU nurses, nurse practitioners, physician's assistants, and neurosurgeons who participated in focus groups (RNs) and semi-structured interviews (NPs/PAs/MDs). Data were analyzed using conventional content analysis to establish categories and themes for each group (RNs, NPs/PAs, MDs). Findings were further evaluated to determine discipline-specific perspectives, and to identify areas of potential practice change.

Results: Twelve RNs, 5 NPs/PAs, and 3 surgeons participated. The RNs, NPs, and PAs described that many different dressing strategies are used. Surgeons expressed that dressing strategies are chosen based on professional experience, amount of hair shaved near the incision, and incision shape and location. Collectively, clinicians identified wound location and patient-related factors influence dressing effectiveness, and had mixed feelings regarding the need for a postoperative dressing outside of the immediate post-operative period. Patient-related perspectives on cranial dressings, including comfort, and sparing hair to aid in the physical and psychological aspects of the recovery process were described by all disciplines. Postoperative dressing management emerged as an area of potential practice change. MDs, NPs, and PAs view dressing management as a cooperative effort amongst the caregivers. Conversely, RNs expressed the desire for more autonomy with post-operative dressing management, especially if dressings fall off. The protocol for postoperative management, aside from time of dressing removal, can be clinician specific and related to wound drainage, though a formal care algorithm has not been developed.

Conclusion: Clinicians described rich, discipline-specific experiences with cranial dressings that are technique and patient-specific. All disciplines gave thoughtful consideration to the patient experience, specifically the patient's perception of the wound and the need for sparing hair to preserve patient dignity. Eliciting perspectives from an interdisciplinary sample of clinicians provides a valuable opportunity to evaluate existing treatment protocols, improve understanding of rationale for practice, and identify opportunities to enhance care delivery. Methods employed in this study may have positive implications for use among interdisciplinary clinician teams caring for other patient populations.

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Suzanne Brodney, PhD, RD, Medicine - General Internal Medicine

A patient decision aid may offer liability protection for a bad outcome after a trial of labor following a prior cesarean birth

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Introduction: We studied the decisions of potential jurors in scenarios where a patient had an adverse obstetric outcome to evaluate if use of a patient decision aid, when choosing between a trial of labor or repeat cesarean after a prior cesarean, reduces medical liability exposure.
Methods: We engaged 54 diverse participants in six focus groups held in Boston, MA. They were asked to role play being jurors in a malpractice trial brought by a patient (plaintiff) against a physician (defendant). The plaintiff alleged harm to the baby because she was not informed about the risks of a trial of labor after a prior cesarean. The jurors heard presentations by experts for the plaintiff and the defendant. Participants were asked to vote on whether the physician met the standard of care, and if not, whether harm resulted. Groups 1 and 2 were presented with three scenarios: no note documenting the discussion about risks and benefits in the medical record (No Note), a note in the medical record (Note), or use of a certified patient decision aid and a note in the medical record (Decision Aid with Note). Groups 3 and 4 considered two scenarios: Note and Decision Aid with Note. Groups 5 and 6 considered three scenarios in reverse order from Groups 1 and 2: Decision Aid with Note, Note, No Note. All votes were anonymous so votes across scenarios are not linked. Fisher's exact test was used to compare the difference in proportions of votes in response to the different scenarios.
Results: Across the groups, the proportion of participants who voted that the defendant met the standard of care was higher in the Note Scenario compared to the No Note Scenario (38/54 [70.4%] vs. 7/35 [20.0%], $p<0.001$). When the Decision Aid with Note Scenario was compared to the Note Scenario, the proportion who voted the defendant met the standard of care with the Decision Aid with Note Scenario was significantly greater than the Note Scenario (53/54 [98.1%] vs. 38/54 [70.4%], $p<0.001$). The results were similar whether focus group members were presented this scenario first, second, or third; or whether the conclusion was based on their initial votes or their votes after discussion with other focus group members.
Conclusion: The use of a patient decision aid conferred substantial liability protection when potential jurors were presented with a hypothetical case of a malpractice claim against an obstetrician after an adverse outcome following a trial of labor after prior cesarean.

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Matteo Buda, MD, Orthopedics

Reoperation Rates after Open Reduction Internal Fixation vs. Primary Arthrodesis of Lisfranc Injuries

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Introduction: Controversy persists as to whether Lisfranc injuries are best treated with operative repair versus arthrodesis. Re-operation rates certainly influence this debate, but prior studies are often colored by the inclusion of hardware removal. The aim of this study was to evaluate patient risk factors associated with re-operation after operative treatment of Lisfranc injuries, excluding implant removal.
Methods: Between July 1991 and July 2016, adult patients who sustained closed, isolated Lisfranc injuries with or without fractures, and who underwent operative treatment with either open reduction and internal fixation (ORIF) or primary arthrodesis (PA), were analyzed. All had at least twelve months of follow up.
Results: Two hundred twenty-three patients met enrollment criteria (mean follow-up: 62.5±42.8 months, range 12-184), of which 168 (75.3%) underwent ORIF and 55 (24.1%) underwent PA. Sixty-nine (30.9%) patients had a second surgical operation for complications without statistical difference between two groups (31% in the ORIF group and 30.9% in PA group, P=1). Excluding hardware removal, 19 (11.3%) in the ORIF group and 5 (9.1%) in the PA group underwent reoperation ($p = 0.8$). Risk factors that reached significance and were predictive of unplanned re-operation included deep infection ($p < 0.001$), delayed wound healing ($p < 0.001$), and non-anatomic post-operative radiographic reduction ($p = 0.02$). Moreover, primary repair was associated with a higher reoperation rate among patients with peripheral neuropathy or with Myerson type C injuries (divergent displacement of the first and lesser metatarsals) ($p = 0.001$ and $p = 0.01$, respectively).
Conclusion: When accounting for planned hardware removal, there appears to be no significant difference in overall re-operation rates between ORIF and PA following Lisfranc injury treatment. Re-operation rates are higher in the setting

of deep infection, delayed wound healing, or non-anatomic reduction after either ORIF or PA. Nonetheless, patients with peripheral neuropathy or Myerson type C injuries appear to benefit from PA.

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Matteo Buda, MD, Orthopedics

Tarsometatarsal Fusion: Are Plates or Bone Graft Really Necessary?

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Introduction: End-stage tarsometatarsal (TMT) arthritis is commonly treated by arthrodesis of the involved joints with fixation hardware consisting of variable combinations of screws, plates, or staples. Furthermore, supplemental bone graft is also frequently utilized. There are limited data that demonstrates superiority of a given fixation method, or the impact of bone graft on fusion rates. The purpose of this study was to determine whether plate fixation or bone graft influences nonunion rates after TMT arthrodesis.
Methods: All patients treated with fusion for TMT arthritis between July 1991 and July 2016 were identified retrospectively. Patients with less than 12 months follow-up, prior midfoot surgery, additional procedures other than TMT arthrodesis with plate or screws, or acute foot trauma were excluded. Patients with radiographic and/or clinical nonunion and those requiring revision surgery were identified. Associated risk factors were detected in each instance via careful chart and radiographic review.
Results: Eighty-eight patients (88 feet, mean follow-up: 75.1±51.4, range 12-179) met enrollment criteria. A total of 189 joints were treated with fusion of which; 67 (35.5%) received plates, 105 (55.6%) received screws alone and 17 (9%) received a hybrid fusion with plates and lag screws. Seventy (79.6%) patients received bone graft without differences between groups ($p = 0.21$). In 60 (68.2%) feet two columns were fused (medial and middle column). Factors independently associated with nonunion were arthrodesis with plate alone (odds ratio [OR] = 5.9, 95% confidence interval [CI] = 1.8 to 19.3, $p = 0.003$) and smoking during the perioperative time (OR = 5.7, 95% CI = 1.6 to 19.6, $p = 0.006$). Bone graft use was a protective factor for nonunion (OR = 0.3, 95% CI = 0.1 to 0.8, $p = 0.01$). Fusion of two columns was a risk factor for postoperative complications (OR = 4.3, 95% CI = 1.4 to 12.8, $p = 0.009$).
Conclusion: For isolated TMT arthritis, plate fusion and smoking are correlated with higher nonunion rates. Use of bone graft results in an increased fusion rate.

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Anne S. Burke, Ph.D., Psychiatry

Resilience training on the college campus for youth at-risk for mental illness: initial effects on well-being and subthreshold psychotic symptoms

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Introduction: The symptoms of psychosis and many other serious mental illnesses typically begin between during late adolescence and early adulthood, i.e., during the late teens and early 20s (McGrath et al., 2008). Thus these disorders frequently emerge during the college years. However, surprisingly, there are currently no empirically-tested mental health screening or early intervention programs that are tailored to college students with early symptoms of mental illness. It has been well-established that interventions delivered early in the course of psychotic illnesses, around the time of the first psychotic episode, can substantially improve outcomes – greatly reducing symptom burden, improving treatment responses and overall quality of life (Criag et al., 2004; Kane et al., 2016; Uzenoff et al., 2012). There is also evidence that such interventions may be even more effective if delivered earlier, before the first psychotic episode has occurred (Ruhrmann et al., 2003; Woodburry et al., 2015). Given this evidence and the absence of validated programs that address this need, we have developed a comprehensive program for college students that aims to: 1) identify students with subthreshold symptoms of psychopathology (which are associated with increased risk for the later development of mental illness (Kessler et al., 2007), and 2) offer these at-risk students a 4-session curriculum providing potentially protective coping skills. In this initial pilot study, we plan to test the hypothesis that the acquisition of these skills leads to improved short-term (i.e., reduction in subthreshold symptoms) outcomes in at-risk college students.

Methods: Participants were screened over two days at a Boston-area university. At the screening, students completed symptoms measures of depression (Beck Depression Inventory; BDI-II) and psychosis (Peters Delusions Inventory; PDI). Students were considered eligible to participate if they exhibited either a BDI score above or equal to 6 or a PDI score above 4 and/or endorsed PDI item 4 or 5 (the persecutory items) and were not receiving any psychopharmacological or psychological treatment currently. Eligible students completed additional questionnaires and then were asked to participate in a 4-session resilience intervention. The intervention, delivered by experienced clinicians, consists of focused training in mindfulness, mentalization capacity (i.e., the awareness of the perspectives of other people) and self-compassion—skills that have been shown to increase resilience during times of stress and adverse life circumstances (Fonagy & Luyten et al., 2009; Neff et al., 2013). Following the intervention, participants completed post-intervention questionnaires.
Results: During the on-campus screening, 153 students were assessed. Of the students screened, 28.0% endorsed some subthreshold symptoms of psychosis or psychosis-like phenomena, typically with delusional beliefs of mild-to-moderate severity (for example, mild paranoia or unusual ideas) and/or perceptual distortions. Also, 46.4% percent of the students described subthreshold or clinical symptoms of depression and 43.8% described subthreshold or clinical symptoms of anxiety, common precursors of serious mental illnesses (Yung and McGorry, 2007). Of those screened, 54.9% were eligible for the intervention. Twenty-three of these students completed the 4-session intervention (divided into two groups of 11 and 12 participants, respectively). Paired samples t-tests compared the pre-post measures and revealed a significant reduction in psychotic symptoms ($t(28)=2.17$, $p<.04$), a marginally significant reduction in depressive symptoms ($t(28)=2.01$, $p=.054$), an increase in mindfulness ($t(28)=-2.38$, $p<.03$), and an increase in two forms of psychological well-being, personal growth ($t(28)=-3.98$, $p<.0001$) and environmental mastery ($t(28)=-3.04$, $p<.01$), in the program participants. Similar screenings and trainings will be conducted over the next two years of the study, with the addition of a wait-list control group, to test the efficacy of the intervention. In addition, the participants' symptoms and functioning will be monitored over time, using both online assessments and objective university data.
Conclusion: The initial, preliminary findings of the first year of this three-year study suggest that the intervention may impact several of the target outcomes. The longitudinal data to be collected will reveal whether the skills acquired during the intervention, and/or other protective factors, produce sustained effects on resilience and functioning.

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Measuring individual physician clinical productivity in an era of consolidated group practices

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Introduction: As physician groups consolidate and value-based payment replaces traditional fee-for-service systems, cardiology practices have greater need to accurately measure individual physician clinical productivity within team-based systems. We compared methodologies to measure individual physician outpatient clinical productivity after adjustment for shared practice resources.
Methods: For cardiologists at our hospital between January 2015-June 2016, we assessed physician productivity by examining completed patient visits per clinical session per month. Using mixed-effects models, we sequentially accounted for shared practice resources (nurse practitioner, fellow and secretary full-time equivalents) and other physician and patient characteristics. We compared mixed-effect and Generalized Estimating Equations (GEE) models based on their predictive performance on a holdout set, and compared mixed-effect, GEE, and Data Envelopment Analysis (DEA) models based on ranking of physicians by productivity.
Results: A mixed-effects model adjusting for shared practice resources reduced variation in productivity among providers by 55% compared to an unadjusted model. The mixed-effects model productivity rankings correlated strongly with GEE model rankings (Spearman 0.99) but mixed-effects outperformed GEE based on predictive power in a holdout dataset (root mean squared error 1.49 vs 2.52; mean absolute error 1.13 vs 1.84, respectively). Mixed-effects model rankings had only moderate correlation with DEA model rankings (Spearman 0.543), though this significantly improved upon exclusion of outliers (Spearman 0.809).
Conclusion: Mixed-effects modeling accounts for significant variation in productivity secondary to shared practice resources. Mixed-effects regression outperforms GEE in predictive power and is less vulnerable to outliers than DEA. This pragmatic methodology can be used more broadly to empower physician practices to deliver higher value care.

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Waijiao Cai, MD, PhD, Neurology

Melanoma-related MC1R is present in human substantia nigra and is reduced in patients with Parkinson's disease

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Introduction: A large number of epidemiological studies have consistently reported a positive, bidirectional link between Parkinson's disease (PD) and melanoma. However, the underlying mechanisms are unknown. Our previous study showed that the melanoma-linked pigmentation gene melanocortin 1 receptor (*MC1R*) influences dopaminergic neuron survival in mice. Loss-of-function variants of *MC1R* have been linked to increased risk of PD. These findings suggest MC1R may play a role in PD. The present investigation is to determine whether MC1R exists in the human substantia nigra (SN) in healthy subjects with no neurological conditions and whether it is altered in patients with PD.
Methods: Postmortem fresh frozen brain tissues from 4 healthy control subjects and 5 PD patients were obtained from the Massachusetts Alzheimer's Disease Research Center, Massachusetts General Hospital. Average age at death was 75.3±16 for controls and 80.8±8 for PD; Average postmortem interval (PMI, hour) was 21.8±17.8 for controls and 16.3±11.4 for PD. All subjects were Caucasian. Tissues were sectioned and stained with anti human MC1R or/and anti tyrosine hydroxylase (TH), a marker for dopaminergic neurons by either peroxidase or florescence immunostaining.
Results: Peroxidase immunostaining demonstrated distinct positive staining for MC1R in SN pars compacta (SNpc), where TH positive dopaminergic neurons were abundant. Cellular morphology revealed membrane as well as intracellular cytoplasmic expression pattern of MC1R that is similar to previously reported in mice. Cell projections are also distinctly stained. Omitting primary or secondary antibody yielded no specific staining but visible pigment. Immunofluorescence staining for MC1R, TH, and nuclear DAPI demonstrated that most TH positive cells were stained positive for MC1R, indicating the presence of MC1R in dopaminergic neurons. There were also MC1R-positive cells that are TH-negative within SNpc. Double florescence staining revealed no overlap of MC1R and GFAP, a marker for glia cells. In all 5 PD patients, there were apparently fewer MC1R-positive cell profiles in SNpc, corresponding to loss of TH-positive cells.
Conclusion: Our results preliminarily demonstrate the presence of MC1R in dopaminergic neurons in the human SN and loss of MC1R-positive cells in PD patients. Further clinical and laboratory studies would help define the functional role of MC1R in dopaminergic neurons and dopaminergic neurodegeneration in PD.

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Signe Caksa, B.Sc. Biochemistry & Molecular Biology, Medicine - Endocrine

Trabecular bone morphology correlates with skeletal maturity and body composition in healthy adolescent girls

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Introduction: Childhood is a critical time for bone accrual and microarchitecture development. Three-dimensional imaging of the distal radius and tibia by high-resolution peripheral quantitative computed tomography (HR-pQCT) has shown that changes in trabecular bone density and microarchitecture in girls are relatively modest across childhood and adolescence. We hypothesized that trabecular morphology would change across this period, becoming more plate-like and thereby conferring increased strength and fracture resistance. We further hypothesized that trabecular bone parameters would be associated with body composition.
Methods: We conducted a cross-sectional study of 86 healthy girls, ages 9-18 years (mean age 14.2 ± 2.6 [SD] years). Exclusion criteria consisted of disorders and medications known or suspected to affect bone. Skeletal maturity was assessed with bone age x-ray. Body composition and areal bone mineral density (BMD) at the lumbar spine were measured by dual-energy x-ray absorptiometry (DXA). We measured volumetric BMD and microarchitecture at the distal radius and tibia by HR-pQCT. Individual trabecula segmentation (ITS) was used to assess trabecular morphology. We used linear and multivariable regression to determine the associations of clinical and biochemical variables with trabecular morphology.
Results: Trabecular bone volume fraction (BV/TV) tended to increase with bone age at the tibia ($R=0.20$, $p=0.065$) though not at the radius. In comparison, plate-like BV/TV (pBV/TV) increased significantly at the tibia ($R=0.41$, $p<0.001$), while rod-like BV/TV (rBV/TV) decreased significantly at both the radius and tibia ($R=-0.34$, $p=0.003$ and $R=-0.28$, $p= 0.008$ respectively) with bone age. The increase in pBV/TV at the tibia was driven by increases in plate number ($R=0.24$, $p=0.026$) as well as plate size, including both thickness ($R=0.52$, $p<0.001$) and surface area ($R=0.43$, $p<0.001$). There was no significant

association of pBV/TV with bone age at the radius, although we did observe a positive correlation with plate surface area (R=0.24, p=0.036). Negative correlations of rBV/TV with bone age were consistent with a decrease in rod number at both the radius and tibia (R=-0.32, p=0.004 and R=-0.27, p=0.012 respectively). To examine the associations of body composition with trabecular morphology, we used multivariable modeling with bone age, height, lean mass, and fat mass as predictors. In this model, lean mass was positively correlated with pBV/TV (β=0.55) and more numerous plates (β=0.56) at the radius, as well as increased plate thickness at both the radius and tibia (β=0.56 and β=0.56 respectively) (p<0.05 for all). In contrast, fat mass was negatively correlated with plate thickness at the tibia (β=-0.23) and plate surface area at both the radius and tibia (β=-0.29 and β=-0.26 respectively) (p<0.05 for all). In addition, lean mass was positively correlated with rod thickness at the radius (β=0.61), while fat mass was positively correlated with rBV/TV (β= 0.31) and rod number (β=0.33) (p<0.05 for all), as well as negatively associated with rod length (β=-0.46, p<0.001), at this site. Serum phosphate positively correlated with total and plate-like BV/TV at both the distal radius (p=0.041 and p=0.011) and tibia (p=0.008 and p=0.008), while PTH positively correlated with total BV/TV only at the radius (p=0.028), and not with rBV/TV or pBV/TV at either site. There were no correlations of 25OHD, 1,25(OH)2D, serum calcium, IGF1 or fasting insulin with trabecular parameters. Both total and plate-like trabecular density at the tibia was significantly correlated with spine BMD (R=0.43, p<0.001 and R=0.56, p<0.001), and while pBV/TV at the radius also correlated with spine BMD (R=0.29, p=0.013), we observed no significant correlation with total BV/TV at the radius. There was no correlation of rBV/TV at either site with spine BMD.

Conclusion: Between the ages of 9 to 18, trabecular morphology changes significantly in healthy girls, with increases in plate-like trabecular density at the distal tibia, plate surface area at both the distal radius and tibia, and additional increases in plate number and thickness observed at the tibia. Conversely, the density of rod-like trabeculae decreases with age at both sites, driven by a decrease in rod number. Lean mass independently correlates with plate parameters at both sites, expected to confer strength, while fat mass correlates with more numerous and shorter rods at the tibia, as well as smaller plates at both the distal radius and tibia. These data suggest that increased lean mass in youth promotes bone strength while increased fat mass may be associated with maladaptive microarchitecture.

Table 1: Correlations of trabecular density and morphology with bone age

Trabecular Parameter	Radius		Tibia	
	R	p	R	p
BV/TV	-0.14	0.238	0.20	0.065
Plate BV/TV	0.06	0.602	0.41	<0.001
Plate Number	0.06	0.824	0.24	0.026
Plate Thickness	0.14	0.235	0.52	<0.001
Plate Surface Area	0.24	0.036	0.43	<0.001
Rod BV/TV	-0.34	0.003	-0.28	0.008
Rod Number	-0.32	0.004	-0.27	0.012
Rod Thickness	0.01	0.928	-0.05	0.655
Rod Length	0.07	0.537	0.26	0.017

Data expressed as (R, p).

Table 2: Multivariable correlations of fat and lean mass with trabecular density and morphology

Trabecular Parameter	Radius		Tibia	
	Fat Mass	Lean Mass	Fat Mass	Lean Mass
BV/TV	-0.01	0.48	0.06	0.47
Plate BV/TV	-0.11	0.55*	-0.05	0.39
Plate Number	-0.05	0.56*	0.21	0.27
Plate Thickness	-0.20	0.56*	-0.26*	0.56*
Plate Surface Area	-0.29*	0.43	-0.26*	0.18
Rod BV/TV	0.11	0.27	0.31*	0.12
Rod Number	0.18	0.19	0.33*	0.16
Rod Thickness	-0.27	0.61*	-0.16	-0.39
Rod Length	-0.21	-0.43	-0.46***	-0.09

Data expressed as standardized regression coefficient (β). All correlations adjusted for bone age and height. *p<0.05; ***p<0.001.

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Catherine Callaway, BA, Psychiatry

Proactive Psychiatry Consultation for Patients with Serious Mental Illness and Cancer: A Pilot Study

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Introduction: Individuals with serious mental illness experience markedly increased cancer mortality in part due to inequities in cancer treatment. Psychiatric treatment at cancer diagnosis may protect against cancer care disruptions. We developed a Proactive Psychiatry Consultation (PPC) intervention for patients with SMI and conducted a pilot trial to assess the feasibility, acceptability, and usefulness of PPC at cancer diagnosis for patients, caregivers, and oncology clinicians.

Methods: From 11/2015-04/2016, 30 patients with SMI (schizophrenia, bipolar disorder, severe major depression) and a recent diagnosis of lung, breast, GI, or head/neck cancer enrolled in a 12-week, single-site pilot study of PPC. PPC is a patient-centered approach incorporating screening for SMI, proactive psychiatry consultation and case management, and co-management with oncology. We assessed the feasibility of patient enrollment and study completion. Exit interviews were performed with patients, their caregivers, and oncology clinicians to assess acceptability and usefulness. We examined changes in clinician-rated psychiatric symptoms over the 12-week study.

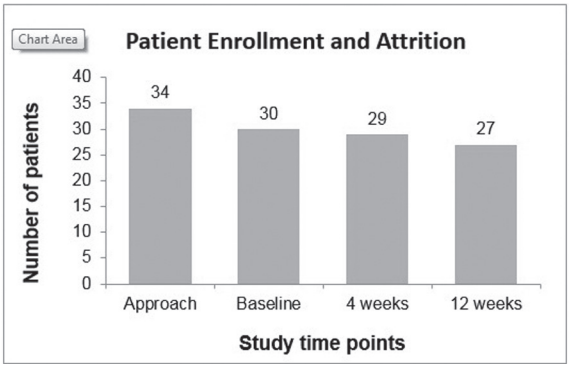
Results: Within 5 months, 88% of eligible patients (or their guardians) consented, and 88% completed all study assessments. Ninety-six percent of patients reported that meeting with the psychiatrist was helpful, and 84% of caregivers shared that PPC addressed the key challenges of caregiving. Nearly all oncology clinicians (93%) evaluated PPC as “very” or “most” useful, and most clinicians (85%) reported that PPC positively impacted cancer care. Psychiatric symptoms improved from

baseline to 12 weeks (t= 2.51, df 28, p=0.02). Five patients who previously refused cancer treatment recommended by their oncologists received cancer treatment after PPC.

Conclusion: Patients with SMI and cancer were able to participate in a trial of a psychosocial intervention with a high completion rate. PPC was feasible, acceptable, and useful for patients, caregivers, and oncology clinicians. Further research is warranted to assess the efficacy of PPC in improving cancer outcomes in this underserved population.

Targeted procedures for patients with serious mental illness and cancer

Barrier	Strategy
Cognitive deficits (fear, paranoia, mistrust)	Verbal consent process using concrete examples and repetition
Need for special protection from coercion	Clinician assesses capacity to consent using validated tool and provides opportunities for discussion
Fragmented care and limited patient and caregiver resources	Person-centered approach with study visits and involvement across settings and systems
Burden of medical and psychiatric symptoms	Joint study with oncology clinicians (or linked to oncology care)



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Stephanie M. Cannistra, BS Candidate, Surgery - Burn

YouTube Fire Challenges: A Qualitative Review

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Introduction: Since its foundation, YouTube has been a place where users share videos of all different genres of content. As YouTube continued to grow and the sheer number of videos uploaded exponentially increased, popular and sometimes dangerous "challenges" began to emerge. These "challenges" were used to increase views and gain subscribers. Participants in the challenge videos, film themselves completing a reckless or potentially harmful task which they then upload to the site in hopes that YouTube fame will follow. However many do not consider the possible repercussions of their actions. As these YouTube "challenges" continued to gain popularity, news outlets across the nation began reporting on the dangers of "challenges." The "Fire spray challenge" is the latest of these challenges, in which a person films themselves lighting an aerosol spray on fire. A patient recently arrived at our hospital with a self-inflicted burn for a YouTube "challenge" entitled "The Fire Challenge." The patient applied an accelerant to his/her skin, and proceeded to light him/herself on fire. This incident prompted the study of three YouTube challenges involving the use of fire play. The purpose of this descriptive study was to determine both the demographics of the participants and amount of different fire-related challenge videos on YouTube. By gathering this information, hopefully it will provide more education about the at-risk population in order to help prevent further burn injuries.

Methods: Between April and May of 2017, three YouTube "'challenges"' involving fire-play were investigated. The three search terms that were used included: (1) Fire spray challenge; (2) Eating a chip on fire; and (3) Eating flaming marshmallows. The same data elements were collected for each video, regardless of the specific search term. These data elements included: (1) Title of video; (2) Date uploaded; (3) Number of views (at time of viewing); (4) Age group, (preschool (2-4 years old), school-age (5-8 years old), tween/preteen (9-12 years old), teenager (13-18 years old), or adult (18+ years old)); (5) Sex; (6) Substance set on fire; (7) Source of flame; (8) Number of bystanders in video; (9) Total Number of attempts (total); (10) Number of attempts after first successful attempt; (11) Injury sustained (if any); (12) Video description; and (13) Video URL. Elements such as age and sex were gathered by observing participants in the complete video. Additionally, outcomes data was not collected as there was insufficient aftermath documentation of these events. Only outward declaration of said injury was documented as an injury. For this study, data was collected from videos within the first 10 pages of search results and repeat videos were only counted once. Relevant videos of this study were determined by the title, stills, descriptions, and watching the complete video to see whether the challenge was attempted or completed.

Results: The "Fire spray challenge" yielded 463,000 results and contained 46 relevant videos (n_1=46). Results from these videos show that 28 (61%) of the participants of this challenge were teenagers, and that 27 (59%) of the participants were female. Additionally, 18 (39%) of the participants used unidentified aerosols as the accelerant, and BIC® pocket lighters were the most common source of flame (30; 65%). 12 injuries were reported, 7 (58%) of which were to the hands. The

majority of these videos (37; 80%) were uploaded in 2016. The "Eating a chip on fire" challenge yielded 519,000 results which contained 37 relevant videos (n_2=37). It was observed that 24 (65%) of the participants were teenagers and that the overwhelming majority of participants were male (35; 96%). In each reviewed video, a potato chip was the object being set on fire, and the most common source of flame was a BIC® pocket lighter (27; 73%). 12 injuries were reported, all of which were to the mouth. The majority of these videos, 26 (70%), were posted in 2014 or earlier. The "Eating flaming marshmallows" challenge yielded 4,770 results. Of the first 10 pages of results, 32 videos were considered relevant (n_3=32). The majority (21; 66%) of participants in this challenge were also teenagers. An impressive 30 (94%) of the participants were male. The fire pit was the most common source of flame (27; 84%) to set the marshmallow on fire. 9 injuries were declared, the majority (4; 44%) of which were to the tongue. Most of these videos, 27 (84%), were posted in 2014 or earlier. The combined data of all three search terms (n=115) revealed that 82 (71%) of participants were male, 31 (27%) were female, and the sex of 2 (2%) participants was unknown. Combined age demographics can be seen in Table 1.

Conclusion: After gathering all of the data from these three different YouTube "'challenges"', it is apparent that the teenagers engage in these behaviors more than any other age-group. However, it must also be noted that the adult age-group is the second most common observed. Participation in "challenges" on YouTube might be skewed due to the amount of video capturing devices that are more accessible to these age groups. Meanwhile, younger age groups might be trying these activities at home. It appears that the "Eating a chip on fire" and "Eating a flaming marshmallow" challenges were more popular in the years 2014 and earlier. Fortunately, their popularity has declined. Now the challenge that poses the most immediate danger is the "Fire spray challenge" due to the large volume of videos posted since 2016. Given the more recent popularity of the "Fire spray challenge", it is important to remind the community of the dangers and possible repercussions of this "'challenge"' in order to prevent future burn injuries.

Table 1: Combined Age Demographics

	Total (n=115)	Percentage
Preteen	16	13.9%
Teenager	73	63.5%
Adult	21	18.3%
Unknown	5	4.35%

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Emily Caplan, BA, Medicine

Partners eCare Research Core for Clinical Research: A pilot to build and test silent BPA notifications for recruiting inpatient study participants

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Introduction: Participant recruitment remains one of the greatest challenges for many research groups. For *An observational prospective study of objective and subjective measures in outpatients with chronic obstructive pulmonary disease to assess clinical deterioration (Emerald-COPD)* at Partners Connected Health, recruiting COPD patients from the inpatient setting was inefficient and low-yielding. To screen for eligible participants, Research Coordinators spent over two hours per day manually searching through the EPIC Reporting Workbench from three hospitals and reviewing admission notes to determine whether patients met eligibility criteria. This pilot project, conducted in collaboration with Partners eCare Research Core (PeRC), examines a new EPIC functionality built to support inpatient recruitment for clinical trials. The silent Best Practice Alert (BPA) system identifies potentially eligible participants in real time to help research teams maximize recruitment accuracy and efficiency of resources.

Methods: This out-of-the-box solution alerts study staff of the inpatient admission of potential participants through EPIC In-Basket messages. The silent BPA notifications detect an event of interest, in this case hospital admissions, using criteria pre-selected by Emerald-COPD research staff. Criteria included: patient class, admit diagnosis, prescribed medications, and presence of COPD on the EPIC problem list; these were used to flag potential participants at multiple Partners hospitals. We hypothesized that this tool would reduce the daily screening time, the number of missed potential participants as well as the time needed to recruit the targeted number of patients.

Results: To date, there have been 171 potentially eligible patients identified through BPA notifications. Of those, we have enrolled 26 participants into the Emerald- COPD study. Since implementation, there have been an average of 3 additional patients each week that were missed during our previous method of screening. In addition to expanding the pool potential participants, this tool has decreased screening time for Research Coordinators. The silent BPA screening method has proven to be 4 times faster than our previous screening method, projected to save 442.5 hours over the duration of the study.

Conclusion: Automation of the recruitment process has allowed us to identify potential participants in real time and avoid missing patients. This has made a substantial impact in raising our enrollment numbers. Silent BPA screening is a considerably faster method which allows for Research Coordinators to devote more time to other important aspects of research such as retention of enrolled participants. When time is allocated effectively, the study can run smoothly and be more cost effective. The outcomes have all been favorable, notably our experience working with the PeRC team. From the build process to implementation, the team was responsive and engaged. This was essential to the speed of production and our encouraging progress. This innovative and instrumental functionality can be specified to the needs of other clinical research groups hoping to utilize EPIC for participant recruitment.

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Lucas C. Carlson, MD, MPH, Emergency

An academic-community collaboration to target community-based programs: Results of a geospatial analysis of asthma-related emergency department visits

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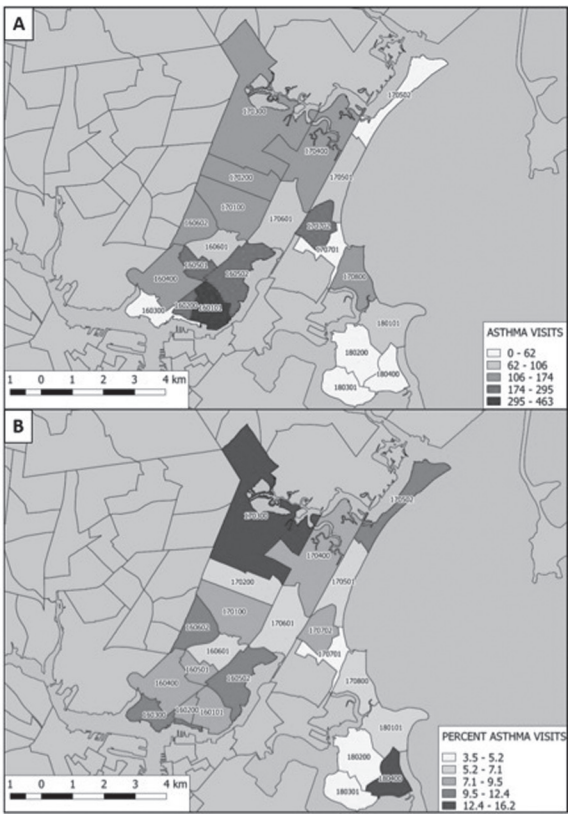
Introduction: Community Action Programs Inter-City, Inc. (CAPIC) is a private, non-profit corporation founded in 1967 to eradicate the root causes of poverty and support families and individuals with complex social needs in the greater Boston area, specifically in the communities of Chelsea, Revere and Winthrop. The emergency department (ED) at the Massachusetts General Hospital (MGH) also serves these communities, and formed a collaborative academic-community partnership with CAPIC to provide analysis of ED visit data to help develop targeted, evidence-based interventions for a variety of health needs. CAPIC identified pediatric asthma as a key issue within the community – a condition that affects over 6 million people under 18 years of age, a disproportionate number of whom live in urban, underserved areas such as Chelsea, Winthrop, and Revere. To support these efforts, we performed a geospatial analysis of pediatric asthma-related ED visits at MGH from within the CAPIC service area.

Methods: We performed a geospatial analysis of de-identified patient record data extracted from MGH ED records of all patients who presented between July 1, 2012 and June 30, 2015. Self-reported home address, chief complaint, diagnosis on discharge from the emergency department, and basic demographics were extracted from the medical record of each visit during this time period. Pediatric asthma-related ED visits were defined as any visit by a patient age 2-12 years (CAPICs service definition) with a chief complaint or discharge diagnosis matching one of the following: “ASTHMA”, “WHEEZING”, or “REACTIVE AIRWAY DISEASE”. Home addresses were geocoded using the US Census Geocoder and aggregated at the census tract level. Choropleth maps were built in QGIS. This work was reviewed and approved by the MGH Institutional Review Board.

Results: There were 298 pediatric asthma-related visits to the MGH ED from the CAPIC catchment area during the study period. Figure 1A shows a choropleth map of pediatric asthma visits per census tract, and Figure 1B shows a choropleth map of pediatric asthma visits as a percent of all pediatric visits. Census Tract 160101 had the greatest number of asthma-related visits, with 40 visits, however, after adjusting for total number of ED visits by census tract, these accounted for only 8.0% of ED visits by this age group within this census tract, similar to that seen in other surrounding census tracts. Census Tracts 170300 and 180400 had the highest proportion of ED visits related to asthma within this age group, representing 14% of visits, although tract 170300 had 24 visits and only seven were from 180400. Census Tracts 170701, 180301, and 180200 had the relatively low percentages of asthma-related visits with 4.6%, 3.3%, and 4.9% respectively.

Conclusion: Our findings indicate that there are large differences in pediatric visits to the MGH ED for asthma among census tracts served by CAPIC. These communities have been accordingly targeted by CAPIC for intervention and further investigation has been initiated to explore lessons from other high-performing communities that were also identified by our analysis. Vast swaths of data are available to and interpretable by healthcare researchers working in academic settings, but for the findings of this work to be effectively harnessed, it is essential that community partners are identified to guide priorities and to ultimately drive impact. We believe that potentially the most effective way to accomplish this is by building and fostering academic-community partnerships such as this.



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Barbara J. Cashavelly, RN, MSN, AOCN, Nursing

Oncology nurses' perceived burnout and perspectives on their relationships with seriously ill patients

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Introduction: Inpatient oncology nurses regularly care for patients at or near the end of life. Given increasing attention to risk of burnout in this setting, we conducted a study to explore nurses' perceived levels of burnout and perspectives on the nature and meaning of their relationships with patients who were seriously ill or dying.
Methods: We conducted in-depth individual interviews with 24 registered nurses (RN)s working on an inpatient medical oncology unit at an academic medical center. Participants completed the 22-item Maslach Burnout Inventory-Human Services Survey (subscales: emotional exhaustion, depersonalization, and personal accomplishment). We then used a semi-structured interview guide to elicit RNs' descriptions of 'good' relationships they had with patients and families with attention to aspects that made these relationships meaningful. Using a framework approach, including an iterative coding process, two team members independently coded all interview data (Kappa=.80) and worked with a multidisciplinary team to identify major and minor themes.
Results: Nurses were 95.8% (n=23) female and 95.8% non-Hispanic white and had a mean age of 32.7 years (SD=10.8 yrs). Median experience as an RN was 4.0 years (range: 1.5-35.0 yrs). Regarding burnout, 20.9% (n=5) reported a moderate to high level of depersonalization; 66.4% (n=16) reported a moderate to high level of emotional exhaustion; and 100% (n=24) reported a moderate to high level of personal accomplishment. In interviews, RNs described specific cases in which they felt they had developed 'good' relationships with patients and families. RN descriptions centered on highly intimate and transformative moments in patient/family care. These unique moments occurred in the context of longitudinal nurse-patient relationships in which RNs felt able to 1) facilitate patient/family processing of emotions and disclosure of treatment preferences that they otherwise were not able to process or disclose to other loved ones or clinicians; 2) provide highly-skilled

patient-centered care to reduce patient suffering; and/or 3) facilitate patient/family prognostic understanding and peace at the end of life. RNs felt privileged to serve these roles. Memorable transformative moments helped to enrich RNs' professional identities and inspire them to continue their work.
Conclusion: Inpatient oncology nurse-patient relationships serve a distinctive function for patient-centered care. These relationships may also foster RNs' sense of personal accomplishment, even in the setting of high frequency of RN emotional exhaustion. Results underscore the importance of assisting RNs in managing patient symptoms, forming longitudinal relationships with patients/families, and coping with conditions that impede 'good' relationships.

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Brittany Chambers, BS, Medicine - Endocrine-Diabetes

Leveraging the Partners HealthCare Primary Care Network for Clinical Trial Recruitment: The GRADE Study

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Introduction: The Partners HealthCare primary care network offers a large patient population for clinical trial recruitment. The population is defined by the primary care practices affiliated with each of several major hospital systems in Eastern Massachusetts. Here, we describe recruitment for an NIDDK-sponsored 37-site multicenter type 2 diabetes clinical trial, The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE; NCT01794143). The Massachusetts site was based at a single institution, Massachusetts General Hospital (MGH). The MGH site used population health management infrastructure to identify eligible patients from the entire Partners HealthCare primary care network. The aims of this analysis were to determine 1) the efficiency of this approach and 2) the yield from each hospital system within the network. We hypothesized that recruitment yield would be highest from the main study site (MGH) but still substantial at other sites (Brigham and Women's Hospital (BWH), Newton Wellesley Hospital (NWH), and North Shore Medical Center (NSMC)).
Methods: Eligible patients were those with type 2 diabetes with HbA1c between 6.8 and 8.5% treated with metformin alone and eligible to start one of four classes of second-step glucose-lowering medications. It was essential to recruit participants before a second glucose-lowering medication was added in the course of usual care, requiring a real-time outreach effort. The initial enrollment target was 150 patients. This was increased to 180 in September, 2016. In order to recruit across the Partners network, we collaborated with investigators based at each hospital system. After obtaining IRB approval, patient lists were generated using TopCare, a population health information management system that contained a diabetes registry, between March 2013 and March 2016. After the introduction of a new electronic health record, Epic, patient lists were generated using an Epic research registry with similar eligibility criteria for the late period of recruitment between October 2015 and March 2017. Primary care providers (PCPs) and endocrinologists were contacted with the assistance of a collaborating investigator within each hospital system for permission to send patients opt-out letters, using a two-letter approach, in which an informational cover letter was signed by the PCP and the recruitment letter was signed by the study principal investigator and collaborating investigator. Health care providers with eligible patients were contacted up to three times. Those who did not respond after these attempts were not re-contacted in subsequent waves of recruitment. For this report, we compiled all TopCare and Epic lists used for recruitment and created a list of all patients identified for attempted contact (the denominator). For the patient dataset, we determined the rate of PCP response, permission to contact, screening rate, and enrollment rate, both overall and by hospital system. We also determined the rate of PCP response to initial outreach by both overall and by hospital system.
Results: The study team sought permission to contact 6,779 patients overall, 5,400 from TopCare and 1,379 from Epic. Health care provider response rate was 72% (Table 1). The health care provider response rate varied across institutions: 85% at MGH (n=418 PCPs), 75.2% at BWH (n=242 PCPs), 65% at NWH (n=143 PCPs), and 35% at NSMC (n=111 PCPs). Eighty percent of patients who ultimately enrolled in the trial were recruited from the Partners primary care network. Twenty-eight percent of patients enrolled from the primary care network came from institutions other then the main site. The number of participants screened and enrolled overall and from each affiliated hospital system is shown in Table 2. Among participants whom PCPs approved for contact, the overall rate of enrollment was 3.4% and did not differ among the hospital systems (P=0.2).
Conclusion: The GRADE study successfully recruited from across the Partners HealthCare primary network in Eastern Massachusetts. While PCP response rates were significantly higher at the primary study site institution, enrollment rates given PCP approval to contact were similar across hospital systems. PCP response and patient screening and enrollment from the other hospital systems enabled the study to exceed its initial enrollment target. Non-response by health care providers to

recruitment queries may limit recruitment outreach. Leveraging population health infrastructure and collaborations across the Partners network are effective strategies for clinical trial recruitment.

Table 1. Rate of health care provider response

	Overall	MGH	BWH	NWH	NSMC	P*
Number of health care providers contacted	914	418	242	143	111	
Health care provider response to study contact, % (n)	72.7% (664)	83.7% (350)	75.2% (182)	65.0% (93)	35.1% (39)	<.0001

* P-value from Chi-Square test

Table 2. Patient-level recruitment data

Total number identified from registries	Overall	MGH	BWH	NWH	NSMC	
%	100%	53.4%	31.6%	8.2%	6.9%	
(n)	(n=6,779)	(n=3,617)	(n=2,143)	(n=554)	(n=465)	P*
Any health care provider response to outreach	70.2% (4761)	79.3% (2867)	62.7% (1343)	65.3% (362)	40.6% (189)	<.0001
Provider permission to contact	58.5% (3966)	68.6% (2483)	50.3% (1078)	48.2% (267)	29.7% (138)	<.0001
Screened	4% (274)	5.4% (194)	2.8% (59)	2.5% (14)	1.5% (7)	<.0001
Enrolled of permission to contact	3.5% (138/3966)	4.0% (99/2483)	2.4% (26/1078)	3.0% (8/267)	3.6% (5/138)	0.2
Enrolled of registry identified patients	2% (138/6779)	2.7% (99/3617)	1.2% (26/2143)	1.4% (8/554)	1.1% (5/465)	0.0002

Screened from other referral sources	82
Enrolled from other referral sources	35
Total enrollment	173

* P-value from Chi-Square test

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Pooja Chandrashekar, Medicine - General Internal Medicine

Impact of a Student-Faculty Collaborative Primary Care Clinic on Emergency Department Utilization: Shifting the Discussion Towards Value-based Healthcare

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Introduction: Many student-run clinics (SRCs) provide primary care to underserved patients who otherwise would pursue more expensive avenues of care such as through visits to emergency departments (ED). Decreasing ED use offers a major opportunity to create value and would be a welcomed justification for funding SRCs. However, few SRCs have rigorously studied this. Many patients in Crimson Care Collaborative (CCC), a network of student-faculty primary care clinics at 6 locations in Massachusetts, do not have primary care access, and are thought to be higher utilizers of the ED. This study estimates the value that CCC creates by identifying the change in ED utilization before and after patients enrolled at the CCC clinic at Massachusetts General Hospital-Internal Medicine Associates (MGH-IMA), and calculating the cost savings to the provider and payer. The effect other covariates may have on ED utilization will also be assessed.
Methods: A retrospective analysis of 767 adult patients who enrolled at CCC-IMA between 9/1/10 and 9/30/16 is being conducted to determine if ED utilization changed after patients enrolled in CCC and had access to primary care. Descriptive analysis will clinically and demographically characterize the annual patient cohorts using Research Patient Data Registry (RPDR) and CCC RedCap survey data. RPDR will also provide ED visits for each patient; the 30 months pre and post enrollment in CCC will be used to estimate the average change. Outpatient clinic visits will be calculated for all patients post-enrollment. Financial data from MGH's internal cost accounting system for FY 2014 & 2015 will be used to calculate the cost and net revenue per ED visit, stratified and weighted by payer, to quantify financial impact to payers and the provider. A regression analysis will evaluate the effect of covariates on the changes in ED use.
Results: Preliminary analysis of ED utilization shows that in the first two years of CCC operation, average ED utilization per patient increased by 14.5% ($p=0.23$) and 52% ($p=0.03$) despite CCC access; however, the subsequent three annual cohorts, 2013-2015, each show an average per patient decrease in ED utilization of 28% ($p<0.001$), 40% ($p<0.001$) and 35% ($p<0.001$). The estimated avoided ED visit cost to the provider (MGH) is estimated at $28.5K, $72.4K, $81.2K for 2013, 2014 & 2015 respectively. The estimated savings to payers for avoided ED visits is estimated at $31.3K, $78.1K, $90.04K for 2013, 2014 & 2015 respectively.
Conclusion: It appears that CCC created value to both payers and the provider from 2013-2015 by providing an alternative source of care. As the CCC SRC program matured, effectiveness of decreasing ED utilization improved. Scheduling lead-times in early years, and other factors may have reduced outpatient access and contributed to early cohort results. Further analysis is ongoing and includes examining outpatient visit volume, in-depth financial analysis, and regression analysis to further our understanding of the value created by CCC.

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Anwesha Chaudhury, PhD, Pathology

White Blood Cell Population Dynamics for Risk Stratification Of Acute Coronary Syndrome

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Introduction: The complete blood count (CBC) provides a high-level assessment of a patient's health, including the inflammatory or immunologic state, and guides the diagnosis and treatment of almost all diseases. Hematology analyzers evaluate CBCs by making high-dimensional single-cell measurements of size, cytoplasmic and nuclear morphology in high-throughput, but only the final cell counts are commonly used for clinical decisions. Here we utilize the underlying single-cell measurements from conventional clinical instruments to develop a mathematical model guided by cellular mechanisms that quantifies the population dynamics of neutrophil, lymphocyte, and monocyte characteristics.

Methods: We develop a dynamic modeling framework adopting methods from the field of statistical mechanics that enable tracking of the evolution of the morphology of white blood cell (WBC) sub-populations as a patient transitions from a healthy to a disease state. These patient state trajectories are quantified by fitting the patient's WBC differential optical scatter to the mathematical model. The patient's risk is thereby estimated using one or a combination of these physiologically-informed parameters.

Results: We show how healthy individuals and hospitalized patients who are indistinguishable based on WBC counts can be robustly classified based on their WBC population dynamics. We use supervised learning techniques to propose an early risk-stratification strategy for patients under evaluation for acute coronary syndrome – potentially enabling earlier therapeutic intervention. In particular, our model can identify more than 75% of patients with initially normal cardiac troponin levels who will be diagnosed with acute coronary syndrome in the subsequent 48 hour period. This assessment was validated in an independent cohort of patients.

Conclusion: This semi-mechanistic modeling framework may enhance screening of patients who present to the emergency room for evaluation of possible acute coronary syndrome. More generally, our study demonstrates how mechanistic modeling of existing clinical data can help realize the vision of precision medicine today.

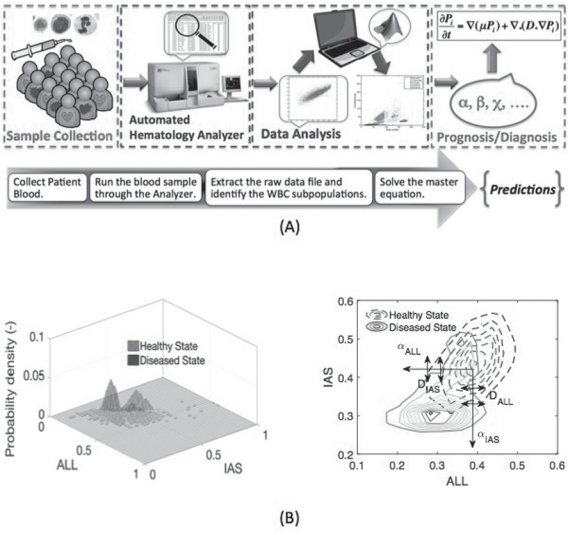

Figure 1: (A) Schematic of the analytical workflow in the practical setting, (B) Probability distribution for the lymphocyte population at the healthy and disease state (within a patient). The contour plot shows how the model captures the trajectory of the distribution for a population of lymphocytes and decomposes it into drift and diffusion, as the blood cell populations are perturbed or altered in response to a pathologic condition.

Figure 2: Predicting which patients with normal cardiac troponin (cTn) will have an elevated cTn in the subsequent 48 hours. (A) Confusion matrix showing the performance of the cross-validated decision tree on the training set. (B) Confusion matrix showing the performance of the cross-validated trained classifier on an independent validation set.

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Jin Yun Chen, Master Degree, Center for Human Genetic Research (CHGR)

Transcriptome analysis and clinical database/biorepository of Alternating Hemiplegia of Childhood patients with *ATP1A3* mutations for potential therapeutic discovery

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Introduction: Mutations in the *ATP1A3* gene have been identified to be prevalent in patients with alternating hemiplegia of childhood (AHC). Over the past twenty years, we have made important contributions towards understanding AHC by establishing a clinical database and linked biorepository. This database contains detailed phenotypic information on over 300 affected individuals and linked biological samples including DNA, RNA, plasma, serum, whole blood, cell lines and CNS tissues. Of the ~300 patients with an AHC phenotype, 56% (168/300) have confirmed *ATP1A3* mutations with a total of 40 unique mutations. Three mutations, located in exons 17, 18 and 21, account for more than 2/3 of all patients with a confirmed ATP1A3 mutation: p.Asp801Asn p.Glu815Lys and p.Gly947Arg. Of the remaining patients, 51 had *ATP1A3* mutations excluded via sanger sequencing of coding exons. To date, no large scale transcriptomic data exist for human-derived AHC samples. The Connectivity Map (CMap) is a database of transcriptional signatures from cell lines treated with chemical and genetic reagents. When paired with the high-throughput L1000 by using a pattern-matching algorithm, the CMap links compounds with disease phenotypes. These CMAP/L1000 tools have helped identify several drug classes or compounds with potential activity for other treatment indications. Examples include the antihelminthic drug parbendazole as an inducer of osteoclast differentiation, the triterpene celastrol as a leptin sensitizer, compounds targeting COX2 and ADRA2A as potential treatments for diabetes, and small molecule therapeutics for skeletal muscular atrophy and spinal muscular atrophy. These tools have also helped to generate new therapeutic hypotheses for the treatment of inflammatory bowel disease and cancer.
Methods: The present work leverages the rich tissue and phenotypic resources in our database/repository and expertise of the microarray analysis and deep sequencing resources at the Broad Institute/MIT. Using the CMap/L1000 tools, we performed a pilot experiment with 31 whole blood RNA samples from AHC patients and 89 healthy control samples.
Results: Our preliminary results revealed differences in the dynamic range of fold-expression achieved per gene in AHC samples when compared to controls. The gene ontology pathways most represented in the AHC gene expression profiles included genes involved in the circulatory system, vascular and embryonic development, as well as in cell proliferation pathways.
Conclusion: Following completion of testing and analyses of the current dataset, we hope to generate hypotheses and perform additional studies in patient derived samples including blood, cell lines, and brain. Identification of unique gene profiles in AHC could help identify novel pathways involved in disease pathogenesis and compounds that could ameliorate the disease phenotype.

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Joey C. Cheung, Psychiatry

Pilot Study of Neurocognitive Changes Associated with Ketamine Treatment for Treatment-Resistant Depression

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Introduction: The relationship between depression and cognitive difficulties is complex (Rock et al., 2013). Depression does not affect all types of memory equally (Burt et al., 1995), as it has the largest adverse effect on episodic memory and a less substantial, but significant, effect on semantic memory. Interestingly, declarative memory and depression both improve with the administration of antidepressants. Studies reliably demonstrate that hippocampal volume is reduced in depressed patients compared to non-depressed controls (Videbech & Ravnkilde, 2015) and this volumetric change is accompanied by impaired memory performance. These changes in hippocampal volume have been attributed to factors such as dendritic retraction, neuronal death, and suppression of adult neurogenesis. Pattern separation is a mechanism for encoding memories, whereby distinct memory representations are created for very similar stimuli and events (e.g., where one parked the car today as opposed to yesterday). It has been proposed that depression negatively impacts pattern separation abilities. However, a link between depression and performance on tasks requiring pattern separation is unclear, despite established evidence that depression is associated with impaired declarative memory. Approximately 30% of patients remain symptomatic despite undergoing adequate courses of evidence-based treatment for major depressive disorder (MDD) (Rush et al, 2009). Ketamine is one promising, fast-acting treatment that has been shown to produce significant and sustained decreases in depression,

even among patients who have failed to respond to other treatments (Zarate et al, 2006), as well as enhanced cognition and memory (Price et al., 2009; Aan het et al., 2010). Animal research suggests that ketamine may exert its therapeutic effects through promoting neurogenesis dependent functions, including pattern separation (Besnard & Sahey, 2016; Sahay et al., 2011). Despite this, ketamine's exact mechanisms of action in humans are not well understood. Improving our understanding of how and why ketamine functions as an antidepressant has the potential of accelerating targeted drug development and to help personalize treatment for MDD. Accordingly, the primary aim of this pilot study is to explore one possible mechanism of ketamine's antidepressant effects: changes in hippocampal activity. Specifically, we administered a behavioral pattern separation task to capture changes in hippocampal activity associated with ketamine exposure among patients with treatment-resistant depression (TRD).

Methods: Data collection is ongoing. For the purposes of preliminary analyses (n=17), we combined samples from two studies. One sample includes patients undergoing clinical intranasal ketamine in addition to antidepressant treatment at MGH (n=6). Another sample (n=11) received a single dose of intravenous ketamine infusion as part of a separate research protocol. The pattern separation task (MST) and Hamilton Depression Rating Scale (HDRS) were administered to all participants prior to receiving ketamine (either intranasal or intraveneous; i.e., "pre-treatment") and following stabilization (either after being on a stable dose of intranasal ketamine two or more weeks or at the four-hour mark post-infusion; i.e., "post-treatment"). For preliminary analyses, descriptive statistics and paired samples T tests were used to analyze the effects of ketamine exposure from pre- to post-treatment on both MST performance and HDRS total scores. Linear regression was used to examine the relationship between pre-treatment HDRS scores and MST performance.

Results: In the sample as a whole (n=17), we observed great variability in overall MST scores at pre-treatment, including across distinct levels of depression severity. Overall MST scores decreased from pre- (M=33.46; SD =19.42) to post-treatment (M=30.39; SD=23.81), reflecting a mild (and non-significant; p=.52) *worsening* of overall memory. With regard to recognition memory specifically, scores increased from pre- (M=0.60; SD=0.32) to post-treatment (M=0.65; SD=0.40), reflecting a mild (and not statistically significant; p=.64) *improvement* in this specific cognitive domain. Depressive symptoms improved significantly from pre- to post-treatment (p<.001). Pre-treatment depression severity predicted magnitude of change in overall memory, such that patients with higher pre-treatment HDRS scores experienced greater improvements in overall MST performance at post-treatment (B=1.85, $F(1,16)=5.50$, R^2=.21; $p<.05$). Additional moderation and subgroup analyses will be presented.

Conclusion: These results provide support for the notion that cognitive functioning (as captured by the MST) and depression are two distinct, albeit related, constructs. Further, pattern separation abilities are highly variable in our relatively severe sample of patients with TRD. Worsened overall memory performance from pre- to post-treatment may be an unstable effect reflective of our (currently) very small sample. The present findings underscore the importance of extending previous work that largely administered the MST among healthy young adults (Liu et al., 2016) to clinical populations in order to better define the cognitive disturbances associated with depression. Findings from this behavioral pattern separation task may provide a basis for future studies examining the structure and functions of the hippocampus using alternative techniques (i.e. fMRI). This line of research has the potential to link ketamine exposure to changes in hippocampal structure, function, cognitive changes, and patient outcomes to advance our ability to better understand and to intervene with TRD.

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Jin Choi, BS, Medicine - Gastroenterology

Neoadjuvant FOLFIRINOX for Patients with Borderline Resectable or Locally Advanced Pancreatic Cancer: Results of a Decision Analysis

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Introduction: With the advent of more effective therapies for metastatic pancreatic ductal adenocarcinoma (PDAC), efforts to incorporate these agents, such as FOLFIRINOX, into the neoadjuvant setting are increasing. However, the efficacy and cost-effectiveness of using neoadjuvant FOLFIRINOX for patients with borderline resectable or locally advanced PDAC are unknown. We performed a decision analysis to assess the value of neoadjuvant FOLFIRINOX versus upfront surgery and adjuvant therapy.

Methods: We developed a mathematical simulation model to evaluate the efficacy and cost-effectiveness of neoadjuvant FOLFIRINOX compared to upfront surgery and adjuvant therapy. We used published and institutional data to estimate model transition probabilities. Model outcomes included overall and disease-free survival, net benefits expressed as discounted quality-adjusted life-years (QALYs), costs in US dollars, and cost-effectiveness expressed as an incremental cost-effectiveness ratio. We used deterministic and probabilistic sensitivity analyses to explore the uncertainty of model assumptions.

Results: Model estimated median overall survival (29 vs 23 months) and disease-free survival (14 vs 13 months) were better for neoadjuvant strategy compared with upfront surgery. Neoadjuvant strategy resulted in an additional 0.68 life-years gained, or 0.57 QALYs, at a cost of $59,000/QALY gained. Sensitivity analysis found that cancer recurrence rates affected model results the most. Our findings were otherwise robust with respect to changes in other model parameters, including chemotherapy toxicity, surgical complications and cancer mortality. Probabilistic sensitivity analyses showed that neoadjuvant strategy was cost-effective 80% of the time with a willingness-to-pay threshold of $100,000/QALY.
Conclusion: Our model results demonstrate that neoadjuvant strategy is preferable to upfront surgery for patients with borderline resectable or locally advanced PDAC from both an efficacy and cost-effectiveness standpoint. Additional clinical data are needed to further define the long-term effectiveness of neoadjuvant FOLFIRINOX to confirm our results.

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Yeon Sook Choi, Ph.D, Dermatology

Preclinical models and therapeutic strategies for treatment of giant congenital melanocytic nevi

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Introduction: Giant congenital melanocytic nevi are virtually always NRAS-driven clonal proliferations of melanocytes that develop in utero independently of UV and may cover up to 80% of the body. The most dangerous consequence of giant nevi is the risk of progression to melanoma. This prompts complete surgical excision of the lesions, producing profound and permanent morbidity. Drug treatments capable of regressing these lesions and minimizing lifetime risk of melanoma could be extremely beneficial to these children.
Methods: We have generated several murine giant nevus models using either constitutive Cre or topical tamoxifen-inducible Cre expression (both melanocyte restricted) to activate oncogenic $NRAS^{Q61R}$ expression from its endogenous promoter. To attain a melanocyte-specific inducible NRAS mutation, Tyr-$CreER^{T2}$ mice were crossed with LSL-$NRAS^{Q61R}$ mice. The Tyr-$CreER^{T2}$ LSL-$NRAS^{Q61R}$ pups were then painted topically with 25 mg/ml 4-hydroxytamoxifen (Sigma# H6278) dissolved in DMSO. To characterize the mouse model and to assess the efficacy of multiple therapeutic approaches, the nevus skin sections were subjected to histological analysis and immunofluorescence with anti-Sox10 (Santa Cruz Biotechnology# sc-17342), anti-S100 (Dako# Z0311), and anti-MelanA (Abcam# ab51061) antibodies as well as anti-MITF (Vector laboratories, VP-M650) and anti-TRP2 (Santa Cruz Biotechnology# sc-10451) antibodies to confirm the ectopic presence of melanocytes. In immune-based treatments, sections were also analyzed for the immune cell recruitment. To generate congenital giant nevi patient-derived xenograft model, human giant nevus tissue has been obtained under an Exempt Human Subjects Research IRB protocol per hospital guidelines (Exemption 4: discarded tissue with no identifiers or other information, except for identification as human giant congenital nevus). All experimental design, sample size and statistical analysis plans have been carried out in consultation with a biostatistician from our Harvard Catalyst Program.
Results: Our NRAS mutation-driven congenital nevus models showed obvious nevus phenotypes which are able to recapitulate histologic and molecular features of human congenital nevi. We also found that these models exhibit a proliferative phase followed by a senescent phase, and transform to invasive melanoma at similar frequencies as in humans (Fig.1). Since therapies may produce distinct efficacies in early/proliferative vs. later/senescent lesions, our NRAS mutation-driven congenital nevus model would be very useful in developing therapeutic approaches to eradicate both actively proliferating nevus cells in neonatal lesions and senescent nevus cells in older children. We have also been examining apparently increased aggressiveness of these lesions in the Mc1re/e red-haired genetic background, as recently suggested for humans. We have begun to apply surgery-sparing, primarily locally administered drug therapies to these models, including: (1) small molecule antagonists of NRAS downstream signaling; (2) immune-based approaches triggering localized inflammation and epitope spreading with vitiligo-like results (Fig.2). Our results demonstrate significant clearance of nevus populations using multiple single and combination approaches, albeit requiring further optimization. We hypothesize that effective, safe therapies for giant congenital melanocytic nevi can be derived from application of the above approaches exploiting key benefits of localized drug delivery. Prevention of melanoma formation can also be tested using our models. To further validate promising approaches in actual living human giant nevi, we now routinely and stably engraft surgically resected giant nevus tissue from children onto immunodeficient mice. These patient-derived human congenital nevus xenografts will be subjected to the best single or combination (non-immunologic) regimens discovered in our studies, thereby permitting rigorous preclinical therapeutic assessments in living human giant nevi.
Conclusion: The results provide distinct histological evidence that our NRAS mutation-driven congenital nevus model recapitulates multiple features of human congenital melanocytic nevi, and also show high incidence of melanoma. Those features mimicking human congenital nevi allow us to use this NRAS mutation-driven nevus mouse model for developing new therapeutic approaches targeting not only proliferating neonatal nevus lesions but also senescent postnatal nevus lesions. Topical combination of MEK inhibitors plus PI3K inhibitors showed a significantly decreased number of melanocytes as well

as more effective depigmentation not long after treatment. In addition to NRAS signaling-targeted therapies, the immune-based approach with squaric acid dibutylester led to localized inflammation and showed melanocyte destruction as well as distinct depigmentation shortly after treatment.

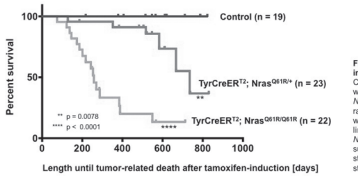

Figure 1. Induced *Tyr*-CreER^{T2} *Nras*^{Q61R} mutant mice with inducible nevi develop melanoma. The majority of *Tyr*-CreER^{T2} *Nras*$^{Q61R/Q61R}$ mice eventually develop melanoma, with median tumor latency of 31.0 weeks. *Tyr*-CreER^{T2} *Nras*$^{Q61R/+}$ mice also develop melanoma, but at about half the rate and with a much longer median tumor latency of 89.3 weeks. Kaplan-Meier survival curves are shown above (green line, *Tyr*-CreER^{T2} *Nras*$^{Q61R/Q61R}$; red line, *Tyr*-CreER^{T2} *Nras*$^{Q61R/+}$; and blue line, control). Comparison of tumor-free survival following 4HT induction of both of these mutant strains against the control group via log-rank test shows statistically significant differences for both groups.

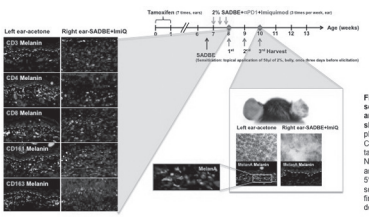

Figure 2. Triple combinatorial immunotherapy with 2% squaric acid dibutylester (SADBE), imiquimod, and anti-PD1 antibody led to localized inflammation and showed distinct depigmentation. To generate nevus phenotypes driven by NRAS mutation, inducible *Tyr*-CreER^{T2} *Nras*$^{Q61R/Q61R}$ newborns were treated topically with tamoxifen, and then all experimental adult mice harboring NRAS mutation-driven nevi were injected IP with anti-PD1 antibody and 2% SADBE was treated topically, along with 5% imiquimod cream. Immune cell recruitment in the squaric acid-treated ear skin was analyzed a week after the first elicitation. Visible depigmentation and melanocyte destruction appeared only 3 weeks after elicitation.

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Georgios Christou, MD, OB/GYN

Are Time-Lapse (TL) Morphokinetic Parameters Useful in Predicting Pregnancy Establishment and Viability? A Retrospective Cohort Study of 223 Women Undergoing in vitro Fertilization with Single Embryo Transfer (IVF/SET)

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Introduction: Certain morphokinetic parameters obtained from preimplantation human embryos cultured in TL- monitored incubators have been evaluated as markers of i) embryonic quality and ploidy status, and ii) embryo's potential for blastocyst formation and implantation. These include either static or interval morphokinetic variables from the early cleavage stage and/or later stages of embryonic development and blastocyst formation. However, it still remains unclear whether blastocysts resulting in live births differ in all or some of these morphokinetic parameters from those appearing morphologically normal but failing to either implant or establish a viable pregnancy. The purpose of this study is to evaluate whether early- or late-morphokinetic parameters predict either pregnancy establishment or viability following IVF/SET.

Methods: *Design*: Retrospective cohort. *Size*: 223 women undergoing IVF/SET at Massachusetts General Hospital Fertility Center. *Duration*: 09/2013-04/2016. *Participants/materials, setting, methods*: Embryos cultured to blastocyst in a TL-monitored incubator and selected for fresh-SET. Conception cycles were compared to non-conception ones, and viable pregnancy cycles were compared to pregnancy failures, in regards to the following early- and late-morphokinetic parameters: time period from i) pronuclei fading (tPN*f*) to 1st cytokinesis (P_1), ii) 2- to 3-cells (P_2), iii) 3- to 4-cells (P_3), and iv) tPN*f* to early blastulation (P_{SB}). *Statistics*: *t*-test, *chi*-square, *one-way ANCOVA* controlling for potential confounders.

Results: Groups did not differ in most of their baseline characteristics (basal FSH, AMH, antral follicle counts; Table 1). Results are presented as marginal means adjusted for maternal age (<38 vs. ≥38 years), basal-FSH, AMH, antral follicle counts and fertilization method (ICSI vs. conventional insemination). In 60.5% (135/223) of cycles ICSI was utilized. Following IVF/SET, 64.1% (143/223) of the women conceived. Of those, 77.6% (111/143) had a viable pregnancy, progressing over 20 weeks gestation. When conception cycles were compared to non-conception ones, no difference was noted in any of the morphokinetic parameters [marginal means (95%CI): 2.53 (2.44-2.62) vs. 2.50 (2.39-2.61), p=0.66; 10.65 (9.99-11.31) vs. 10.52 (9.70-11.33), p=0.81; 1.19 (0.77-1.62) vs. 1.13 (0.60-1.67), p=0.86; 68.63 (67.27-70.00) vs. 69.48 (67.64-71.32) hours, p=0.48; for P_1, P_2, P_3, and P_{SB}, respectively]. Similarly, when viable pregnancy were compared to pregnancy failure cycles, morphokinetic parameters did not predict the outcome of the pregnancy [marginal means (95%CI): 2.57 (2.46-2.66) vs. 2.44 (2.23-2.66), p=0.31; 10.57 (10.00-11.02) vs. 10.73 (8.76-11.94), p=0.83; 1.15 (0.81-1.57) vs. 1.52 (0.61-2.83), p=0.63; 69.28 (67.85-71.12) vs. 66.66 (63.32-69.85), p=0.23; for P_1, P_2, P_3, and P_{SB}, respectively].

Conclusion: In a group of unselected infertile patients undergoing fresh-IVF/SET, early-cleavage morphokinetic parameters and time to early-blastulation did not predict reproductive outcomes.

Table 1. Baseline and cycle characteristics of the study population.

Characteristic	Non-Conception Cycles n = 80	Conception Cycles n = 143	p-value
Age, years	34.8 (32.5, 36.9)	33.4 (31.4, 35.6)	0.02
Body Mass Index, kg/m2	23.8 (21.5, 27.8)	22.7 (20.5, 26.0)	0.09
Basal FSH, IU/L	6.5 (5.6, 7.9)	6.7 (5.6, 8.2)	0.77
Antral follicle count, n	13.0 (10.0, 20.0)	15.5 (11.3, 23.8)	0.07
AMH, ng/ml	2.7 (1.6, 5.0)	2.9 (1.5, 6.8)	0.49
Infertility Diagnosis, n (%)			0.77
Idiopathic	20 (25.0)	28 (19.6)	
Anovulatory	1 (1.3)	6 (4.2)	
DOR	6 (7.5)	11 (7.7)	
PCO	3 (3.8)	3 (2.1)	
Tubal factor	6 (7.5)	12 (8.4)	
Uterine factor	0 (0.0)	0 (0.0)	
Endometriosis	2 (2.5)	4 (2.8)	
Male factor	30 (37.5)	56 (39.2)	
Other (family planning, non-infertile)	3 (3.8)	3 (2.1)	
Combined factors	9 (11.3)	11 (7.7)	
Fertilization Method, n (%)			0.01
ICSI	39 (48.8)	96 (67.1)	
Conventional insemination	41 (51.3)	47 (32.9)	

Abbreviations: FSH, follicle stimulating hormone; AMH, anti-müllerian hormone; ICSI, intracytoplasmic sperm injection; DOR, diminished ovarian reserve; PCO, polycystic ovaries; IQR, interquartile range. Values are presented as median (IQR) unless otherwise noted.

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Jacqueline N. Chu, MD, Medicine

Surgical vs. Endoscopic Management of T1 Esophageal Adenocarcinoma: A Modeling Decision Analysis Incorporating Age and Comorbidity

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Introduction: Treatment of mucosa-limited esophageal adenocarcinoma (i.e. T1a) has moved increasingly from esophagectomy to endoscopic therapy (ET). However, tumors with submucosal invasion (i.e. T1b) are largely considered too high-risk to be treated with ET. We investigate the effectiveness and cost-effectiveness of esophagectomy versus ET for T1a and T1b esophageal adenocarcinoma and the effect of age and comorbidities on these outcomes using a decision analytic Markov model.

Methods: The base-case model simulated a hypothetical cohort of 75 year old men with Charlson comorbidity index of 0 and either T1aN0M0 or T1bN0M0 esophageal adenocarcinoma (Fig 1). The two treatment strategies compared were esophagectomy and serial ET. Patients in the model could die from procedure, die from background mortality (based on age and comorbidity index), or die from cancer and were followed until death. Risk of surgical mortality was estimated with the Steyerberg risk score, which incorporates age and comorbidities. Sensitivity analysis was performed for key model variables such as age 60-85 at diagnosis and comorbidity indices of 0-2, as well as costs and quality of life utilities. Post-treatment risk of cancer-specific death was derived from the SEER-Medicare database. Outcome measures were unadjusted life years, quality adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs). The willingness to pay threshold was set at $100,000/QALY.

Results: In the T1a base case, esophagectomy yielded slightly more unadjusted life years compared to ET, but fewer QALYs (Fig 2a). This result was not sensitive to age at diagnosis or comorbidity index, but was sensitive to relative utilities of post-esophagectomy and post-ET health states. In the T1b base case, esophagectomy yielded more unadjusted life years and QALYs compared to ET, but was not cost-effective with an ICER of $156,981. Combinations of age and comorbidity index changed the optimal therapy with regard to both QALYs (Fig 2b) and cost-effectiveness. The T1b model was also sensitive to relative utilities of post-esophagectomy and post-ET health states. The key determinants of the preferred strategy in the analysis included comorbidity index, age when combined with comorbidity index, and utilities of post-esophagectomy and post-ET health states.

Conclusion: Our analysis confirms that for T1a esophageal adenocarcinoma, ET yields slightly fewer unadjusted life years but more QALYs, and dominates esophagectomy with regard to cost-effectiveness for all ages and comorbidity indices tested. In contrast, the preferred therapy for T1b esophageal adenocarcinoma depends on age and comorbidity index due to risk of surgical mortality and competing risk of non-cancer related death. For both T1a and T1b esophageal adenocarcinoma, a key

determinant of the optimal treatment strategy was post-treatment utilities, suggesting that a patient's preferences regarding quality of life post-esophagectomy versus ET is critical. Our analysis thus finds that treatment for T1b esophageal adenocarcinoma should be an individualized decision factoring in the patient's combination of age and comorbidities, and that treatment for both T1a and T1b esophageal adenocarcinoma should take into consideration the patient's quality of life preferences.

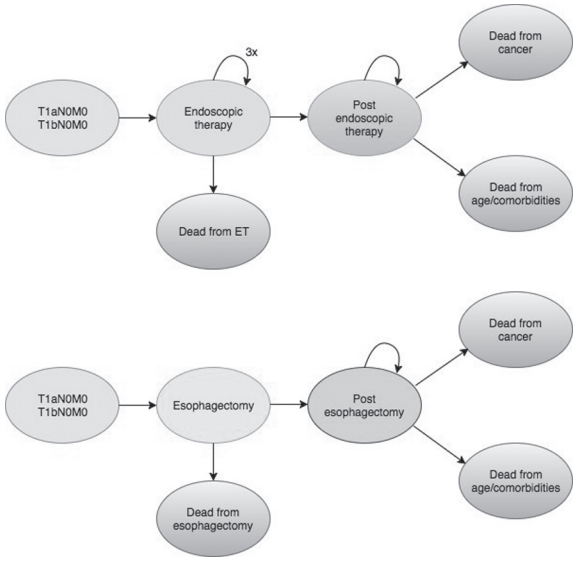

Figure 1. Simplified schematic of two treatment strategies for T1a and T1b esophageal adenocarcinoma, endoscopic therapy (ET) and esophagectomy, and possible transition states.

A)

Therapy	Cost, US$	Unadjusted life-years	QALYs	ICER, US$
T1a				
Esophagectomy	47,812.09	8.31	4.95	Dominated
ET	12,977.74	8.05	5.22	
T1b				
Esophagectomy	46,345.74	6.68	4.07	156,980.91
ET	11,366.51	5.77	3.85	

B)

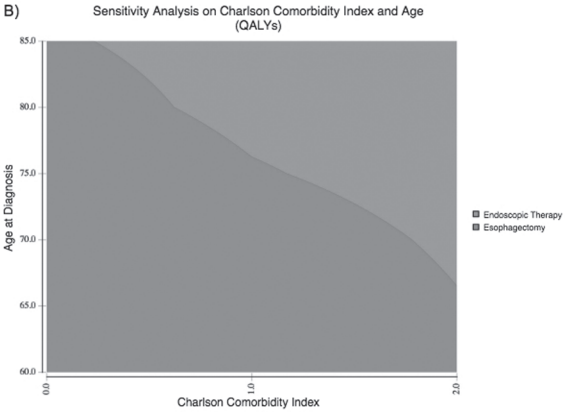

Figure 2. A) Results for base-cases of 75 year old man with T1a or T1b esophageal adenocarcinoma. B) Two-way sensitivity analysis of Charlson comorbidity index and age effect on QALYs for the T1b model.

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Kristina Cieslak, MD, Psychiatry

Integrated Diabetes Management for Individuals with Serious Mental Illness

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Introduction: Premature mortality due to cardiovascular disease in those with schizophrenia is the largest lifespan disparity in the US and is growing; adults in the US with schizophrenia die on average 28 years earlier than those in the general population. An estimated one in five people with severe mental illness (SMI) has diabetes; lifetime rates of diabetes among those with schizophrenia are two to three times higher than for those in the general population. Contributing factors to this astonishingly high rate of diabetes include effects of antipsychotic medication, unhealthy lifestyle, and likely factors related to schizophrenia itself. High rates of tobacco dependence and poor understanding of diabetes management combine to cause to the extraordinarily high morbidity and mortality associated with diabetes in those with SMI. Importantly, though those with SMI may have lower diabetes-specific knowledge, they are receptive to medication, disease self-management strategies, and weight loss programs when provided. One large study found *greater* adherence to oral hypoglycemic medications among diabetes patients with than without comorbid schizophrenia.
Methods: We have developed a 16-week tailored behavioral and educational group intervention for individuals with schizophrenia and diabetes, utilizing the concept of 'reverse integrated care,' bringing medical intervention into the community mental health setting. Core features of this intervention include motivational interviewing, basic education, and problem-solving. **Primary Outcomes (measured at 0, 8, and 16wks):** - Glycemic control, as measured by HbA1c - Cholesterol Measures of diabetes knowledge and self-management - Brief Adherence Rating Scale Score - Short Diabetes Knowledge Instrument Score - Summary of Diabetes Self-Care Activities Score - Problem Areas in Diabetes Score **Secondary measures (measured weekly):** Blood pressure, Weight, Step count **Topics of Behavioral Group Intervention** Module A: What does diabetes mean for me? / Blood sugar (2wks) Module B: Diet (3wks) Module C: Exercise/Weight loss (3wks) Module D: Medications, practical aids to medication adherence (2wks) Module E: Stress management with referral to smoking cessation

resources for smokers (3wks) Module F: Positive psychology/empowerment (2wks) Review: Review of key concepts and practical applications (1wk)

Results: Thirty individuals were consented and randomized to a two-period crossover design consisting of a 16-week group intervention and a 16-week observation period. Average HbA1c = 7.5, range = 5.9-13.4. The first intervention group began in early February, the second group in June, 2017. Common identified barriers – healthy food too expensive, not cooking, lack of healthy options eating out, lack of exercise, sugar-containing beverages, low diabetes knowledge. Participants in Group 1 (n=9) demonstrated change from baseline to the end of the 16-week group total cholesterol (-21.74 mg/dl), triglycerides (-106.3 mg/dl), weight (-4.28 pounds), diastolic blood pressure (-12.1 mmHg), systolic blood pressure (-9.3mmHg), and HbA1C (-0.1). Three of nine participants lost between 10 - 15 pounds. Promising increases were seen in average total step count (4012 steps), HDL (1.8 mg/dl), diabetes knowledge questionnaire (1.56 points), total exercise (4.72 points), diet (6.09 points), and foot care (2.73 points). End of treatment total cholesterol and diastolic blood pressure were significantly improved from baseline ($p<0.01$). Comparing active treatment with waitlist control from weeks 0-16, there were significant group by time effects on total cholesterol ($p<0.01$) and diastolic blood pressure ($p<0.05$). At the current time, the second group (n=9) has reached the mid-point of their active intervention. Early results are extremely promising; average weight loss among members is 12.55 pounds, and A1C has dropped an average of 1.2 points.

Conclusion: There is a pressing need to address the morbidity and premature mortality related to modifiable health behaviors in this underserved population, yet individuals with SMI and diabetes are much less likely to be identified or to receive recommended diabetes care and monitoring. Failure to identify and treat diabetes in this population equates to a preventable cost of approximately eight billion dollars to the healthcare system. We hope to further establish and refine a standard of care diabetes education curriculum, tailored for individuals with SMI, a population with high prevalence of diabetes but low rates of diabetes diagnosis, education, and treatment, resulting in disproportionate diabetes-related medical morbidity and premature mortality. Results from year one demonstrate this program to be easily implementable, well-accepted, socially relevant and effective.

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Amanda B. Coakley, PhD, Nursing

The Effect of 2 Surgical Splinting Pillows on Pain and Pulmonary Status after Kidney Removal

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Introduction: Post-operative nephrectomy patients experience discomfort at the surgical incision preventing deep breathing and removal of pulmonary secretions. Splinting reduces the stress on the incision by equalizing the pressure across the incision and facilitates comfortable aeration of the lungs preventing pulmonary complications, but little is known of the effect of splinting devices as a strategy for pain management and deep breathing. The purpose of this study was to compare the effects of a therapeutic pillow versus the standard of care pillow on pain, in post-operative nephrectomy patients as measured by pain perception, pain medication use.

Methods: Post-operative nephrectomy patients were randomized to receive treatment (therapeutic pillow) or standard of care (a bath towel rolled into a pillow for deep breathing). Patient sex and type of nephrectomy were collected, and the McGill Pain Questionnaire and visual analogue scale for pain or the Present Pain Intensity were complete on day 1 and 2 post-op. Patients were also asked open-ended questions related to the use of the pillow intervention, including comfort and ease of use. Quantitative data were analyzed using the Mann Whitney U test, and qualitative data were analyzed using content analysis.

Results: 52 subjects, 37males and 15 females, mean age of 56.3 ± 14 years, were randomized into treatment (n= 23) and standard of care (n= 29) group. 37 patients had a laparoscopic partial nephrectomy and 15 had open total nephrectomy. There were no statistically significant differences between the treatment and standard of care group on the McGill Pain Questionnaire, or the visual analogue scale for pain or the Present Pain Intensity on post-op day 1 or 2. However, there were consistently lower pain scores in the treatment group on day 1 and day 2, compared to the standard of care group. One theme was identified from the qualitative data that described patient's perception of reduced pain when coughing and deep breathing when using the therapeutic pillow intervention.

Conclusion: Although pain scores did not differ significantly between the groups, nephrectomy patients found that the therapeutic pillows were beneficial, and helpful when coughing and deep breathing. Future research is needed to determine if the therapeutic pillows will be a beneficial adjunctive or alternative treatment strategy to improve comfort in postoperative nephrectomy patients.

Holly Milotte, PI with the Shumsky Kidney Pillow

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KC Coffey, MD, MPH, Medicine - Infectious Diseases

Endoscopic Retrograde Cholangiopancreatography Associated with Ceftriaxone-Resistant *Escherichia coli* Bloodstream Infections: Looking for Hay in a Haystack

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Introduction: Contaminated duodenoscopes used in endoscopic retrograde cholangiopancreatography (ERCP) have been implicated in carbapenem-resistant *Enterobacteriaceae* infections. Multi-locus sequence typing (MLST) can identify outbreaks with rare pathogens, but it is unclear how well it can link transmission of common *Enterobacteriaceae*, e.g. ceftriaxone-resistant (CRO-R) *Escherichia coli*. Our Infection Control Unit (IC) was alerted to a suspicious number of CRO-R *E. coli* bloodstream infections in patients who had undergone ERCP in the Spring of 2014. IC investigated an association with duodenoscopes and made recommendations for surveillance and reprocessing in accordance with CDC guidelines.
Methods: We identified all blood cultures positive for CRO-R *E. coli* collected January 2014–June 2015. A case was defined as the first CRO-R *E. coli* positive blood culture from a unique patient who had undergone ERCP within 90 days prior. Controls were CRO-R *E. coli* blood cultures from patients who did not undergo ERCP or did so after bacteremia. Duodenoscopes used for ERCP were abstracted from the medical record. We evaluated clonal relationships by MLST and single nucleotide polymorphism (SNP) profiles. Resistance gene and mobilizing vector analysis provided strain resolution.
Results: We identified 52 blood cultures positive for CRO-R *E. coli* during the study period. Twenty-eight met the case definition and 11 were controls. Thirty of the 39 isolates belonged to MLST-131. Eleven of these isolates were from patients exposed to the same duodenosope within 90 days prior to bacteremia. CTXM-15 mediated CRO-R in 10 of the exposed cases. The odds ratio of bacteremia with *E. coli* MLST-131 if exposed to this duodenoscope was 4.6 but was not statistically

significant (95% CI 0.5-42.1). Hamming distance SNP trees showed common ancestry but not clonality among the cases (separation <500 chromosomal SNPs, <1000 plasmid SNPs).
Conclusion: The implicated duodenoscope was removed from use despite inability to confirm clonality. The study was underpowered to demonstrate statistical significance because our cases involved highly prevalent strains of CRO-R *E. coli.* While genomic analyses can identify epidemiologic associations, in outbreaks due to common pathogens a high level of suspicion should dictate intervention.

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Drew C. Coman, Ph.D., Psychiatry

Predictors of Symptom and Functional Outcomes in Young Adults Treated for Two Years in a First Episode Psychosis Program

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Introduction: Specialty first episode psychosis (FEP) treatment programs are relatively new in the U.S. Characterizing the early recovery patterns of patients with FEP treated in these programs, and identifying factors associated with recovery, is important as we learn how to improve the long-term course of psychotic disorders (Azrin, Goldstein, & Heinssen, 2015). Specialty FEP care is associated with greater improvements in symptoms and functioning (Kane et al., 2015) and lower hospitalization rates (Srihari et al., 2015) than usual care. However, the trajectories of early recovery vary widely for patients offered specialty care. For example, in one study that prospectively examined recovery over the first 5 years of treatment, only 14% were fully recovered, and while almost half of patients achieved a 2 year period of symptom remission, only a quarter achieved sustained adequate social and vocational functioning (Robinson, 2004). Several disease-related and individual variables contribute to these variations. Specifically, earlier age of onset has been associated with poorer outcomes (Malla, 2005). Longer duration of untreated psychosis (DUP) has been found to be associated with and/or a moderate patient outcomes, such as increased severity of symptoms, decreased quality of life, and poorer social functioning (Kane et al., 2016; Marshall, 2005; Perkins, 2005). Substance Use Disorders (SUDs) are also common and patients who misuse cannabis have been shown to have higher rates of non-adherence to medications, more severe symptoms, poorer psychosocial functioning, and re-hospitalization (Clausen et al., 2014; Colizzi et al., 2016; Ranganathan, Skosnik, & D'Souza, 2016). Finally, a lack of family involvement in treatment correlates with poorer patient outcomes (Lenior, 2001). We conducted a retrospective medical chart review of patients who had a psychotic episode and were treated at the MGH First Episode Psychosis Program (FEPP). The aims were to: a) characterize the sample of FEP patients who remained in specialty first episode care for at least two years; b) describe the trajectory of symptomatic and functional recovery over this time period; and c) identify clinical and demographic predictors of outcomes. We hypothesized that patients would show reductions in depression, substance use, and positive and negative symptoms. Additionally, we hypothesized that patients would show improvement in functional outcomes (i.e., rates of employment and school attendance) and in Global Assessment of Functioning (GAF) scores. Lastly, we hypothesized that younger age of onset, longer DUP, SUD at initial intake, and less family involvement would predict poorer symptom and functional outcomes.
Methods: Medical chart reviews were conducted on 60 patients aged 13 to 38 (63.3% male) with a primary psychotic disorder who completed two years of treatment at the MGH FEPP, a specialty care, outpatient clinic consisting of an interdisciplinary staff of psychiatrists and a psychologist. Patients with a diagnosis of an affective psychosis or autism were excluded. Study staff reviewed records and extracted relevant information from the time of initial evaluation (IE), one year later (Y1), and then at a two year follow-up (Y2). All patients were offered psychopharmacological treatment, CBT, and family psychoeducation based on the RAISE NAVIGATE Program (Mueser et al., 2015). Statistical analyses included nonparametric tests, paired sample t-tests, one-way and repeated measures ANOVAs, and logistic and general linear regression models.
Results: While the number of patients with a SUD persisted over time (IE: 28.8% to Y2: 37.3%), relative to the IE there were significantly fewer patients with clinical depression (10.1% decrease), negative (11.8% decrease), and positive symptoms (28.8% decrease) by Y2. More patients were employed (32.2% increase), enrolled in school (17% increase), or either working or in school (32.2% increase) by Y2. GAF ratings increased significantly over time, Wilks's $\Lambda = 0.45$, $F(2, 41) = 25.03$, $p < .001$, multivariate $\eta^2 = 0.55$. Post hoc tests revealed that GAF ratings were significantly increased from EI to Y1 and Y2, though were not different from Y1 to Y2, indicating that most of the improvement occurred in Y1. Age of onset was correlated with GAF ratings at Y1 (Pearson $r(39) = 0.34$, $p = 0.01$) and Y2 (Pearson $r(37) = 0.28$, $p = 0.04$). While controlling for depression, shorter DUP was associated with a lower likelihood of depression at Y1, χ^2 (2) = 7.32, p = .03 (OR = 1.0; CI = 1.0-1.01; p = 0.02) and at Y2 (χ^2 (2) = 12.93, p = .002, OR = 1.0; CI = 1.0-1.01; p = 0.004). The non-SUD group's GAF

ratings improved across *all* time point comparisons (p value = 0.01 to < .001); however, within the SUD group, GAF ratings did not significantly improve from T1 to T2, $t(13) = 0.053$, $p = .96$. Patients with any family involvement and those without both experienced significant increases in GAF ratings from IE to Y2 (p value = 0.02 to < .001); however, only the group with family involved experienced improvements from IE to Y1, $t(34) = -4.78$, $p = < .001$.

Conclusion: Over a two year treatment period, FEP patients showed improvements in symptoms and functioning. This suggests access to specialty, interdisciplinary, comprehensive care in FEP is vital for patients, as it can positively impact symptoms and functional outcomes. Shorter DUP predicted a lower likelihood of depression at both follow-up time points, suggesting delays in entry to treatment may be related to persisting mood difficulties, even with specialty care. Negative symptoms and substance use appear less responsive to the treatment and persistent SUD may place a "ceiling" on patients' recovery. Given this and the refractory nature of both SUD and negative symptoms observed, it may be important for FEP specialty care clinics to integrate evidence-based substance use interventions and social skills programming for negative symptoms. Family involvement may also serve as a catalyst to recovery.

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James W. Connelly, BA, Orthopedics

Indications for MARS-MRI in Patients Treated with a Recalled Metal-on-Metal Hip Arthroplasty

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Introduction: Adverse local tissue reaction (ALTR) is a major cause of revision surgery in metal-on-metal (MoM) hip arthroplasty and is most accurately detected by metal artifact reduction sequence magnetic resonance imaging (MARS-MRI). Currently, there is no strong consensus on when to take MARS-MRI in MoM patients. Our primary objective was to identify which patient demographic and clinical factors were predictive of ALTR in patients treated with a subsequently recalled MoM hip replacement system, and use these prognostic variables to create effective algorithms for pre-screening patients for MARS-MRI. Our secondary goal was to compare our algorithms to existing national and literature-suggested guidelines on when to take MARS-MRI in MoM hip arthroplasty patients.

Methods: The study cohort consisted of 145 MoM total hip arthroplasty (THA) and 182 MoM hip resurfacing arthroplasty (HRA) patients from a larger prospective, multicenter follow-up study of a recalled hip system. All patients had unilateral MoM implants and MARS-MRI performed at a mean of 7.0 years (range, 3.3–12.2) from surgery regardless of clinical presentation. Anderson classifications of C2 and C3 were considered ALTR positive, and C1 and nonexistent ALTR were considered ALTR negative. Univariate tests were conducted separately for each implant group with ALTR presence and all relevant demographic, radiographic, and clinical variables. Based on our univariate results, multivariate analysis was performed for each implant group using ALTR presence as the dependent variable. Variables that proved predictive of ALTR in the multivariate models of each implant cohort were included in their respective algorithm. Clinically useful cutoff values for continuous predictors were determined using receiver operator characteristic (ROC) analysis with ALTR presence as the outcome. Implant groups were split by sex for ROC analysis if sex was significant in the multivariate analysis. We then crafted highly sensitive algorithms for predicting ALTR and indicating MARS-MRI in our two patient cohorts by using the ROC-generated cutoff values. The proposed implant-specific algorithms and several previously established national and literature guidelines for when to take MARS-MRI in hip arthroplasty patients were applied to our dataset via ROC analysis and compared by area under the curve (AUC), sensitivity, and specificity.

Results: Forty-nine of 145 (33.8%) MoM THA patients in our cohort were ALTR positive. In univariate analysis, VAS pain (p=0.046), blood Co levels (p=0.003), and Co/Cr ratio (p=0.010) were the only variables associated with ALTR in MoM THA. Multivariate analysis yielded VAS pain ≥ 2 (OR=2.210; p=0.044), high blood Co (OR=1.053; p=0.015), and male sex (OR=2.371; p=0.028) as predictors of ALTR presence. ROC analysis of VAS pain yielded 0.75 as a cutoff value for both males (84.2% sensitivity, 23.1% specificity) and females (56.7% sensitivity, 54.5% specificity). Blood Co level cutoffs were determined to be 2.60 ppb for men (70.0% sensitivity, 38.1% specificity) and 4.80 ppb for women (68.4% sensitivity, 63.5% specificity). Twenty-nine of 182 MoM HRA patients (15.9%) had moderate or severe ALTR. Blood Co (p<0.001) and Cr (p<0.001) were the only variables associated with ALTR in univariate analysis of the MoM HRA patients. High blood Co (OR=1.070; p=0.011) and high blood Cr (OR=1.162; p=0.002) remained the only significant predictors of ALTR presence in multivariate analysis. The ROC-generated cutoffs were 1.15 ppb for Co (89.7% sensitivity, 49.0% specificity) and 1.17 ppb for Cr (89.7% sensitivity, 43.1% specificity). The novel algorithms considering sex, blood Co, and VAS pain for MoM THA and blood Co and Cr for MoM HRA were constructed based on our cutoffs and combined in Figure 1. When applied to our dataset, our algorithms showed higher predictive capability for ALTR than existing national and literature guidelines for when to take MARS-MRI in other MoM and metal-on-polyethylene (MoP) hip implants based on AUC, sensitivity, and spec-

ificity (Table 1). The proposed MoM THA algorithm showed an AUC of 0.618 and sensitivity and specificity of 91.5% and 32.2%, respectively. The algorithm for MoM HRA achieved 96.6% sensitivity and 35.3% specificity with an AUC of 0.659.
Conclusion: In MARS-MRI at midterm follow up, we found that VAS pain, blood Co levels, and male sex were predictive of ALTR in MoM THA, and blood Co and Cr were predictive of ALTR in MoM HRA. We used these predictive measures to craft decision tree algorithms that achieved higher sensitivity and comparable specificity to previously proposed national and literature guidelines on when to take MARS-MRIs in our study cohorts.

Table 1: Receiver operating characteristic (ROC) analysis area under the curve (AUC), sensitivity, and specificity of existing guidelines and the proposed decision tree algorithms with adverse local tissue reaction as outcome.

Implant Type	Guideline	AUC	Sensitivity	Specificity
MoM THA	Proposed MoM THA	0.618	0.915	0.322
	National MoM THA 1	0.603	0.872	0.287
	National MoM THA 2	0.580	0.447	0.759
	Literature MoP THA	0.609	0.723	0.494
MoM HRA	Proposed MoM HRA	0.659	0.966	0.353
	National MoM HRA 1	0.621	0.517	0.725
	National MoM HRA 2	0.636	0.586	0.686
	Literature MoM HRA	0.586	0.793	0.379

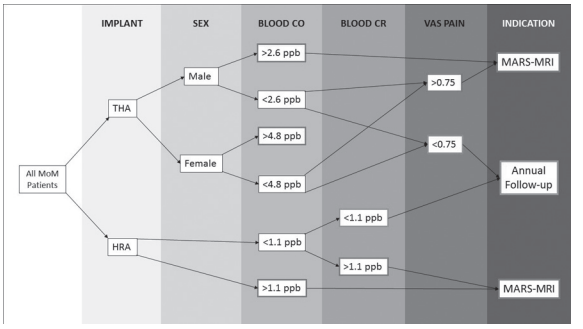

Figure 1: Proposed decision tree algorithm for when to take MARS-MRI in patients treated with MoM THA and MoM HRA devices.

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Katherine Crawford, BS, Center for Human Genetic Research (CHGR)

The Cerebrovascular Disease Knowledge Portal: An Open Access Data Resource to Accelerate Genomic Discoveries in Stroke

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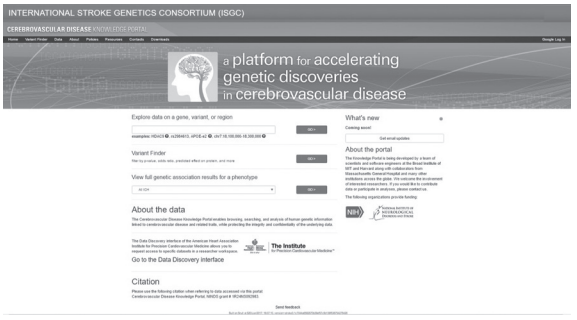
Introduction: Stroke is a leading cause of death and disability across the globe and represents an archetypical common complex disease with, both genetic and environmental determinants contributing to its occurrence. Genetic association studies seek to identify these variants and link them to specific genes, which, in turn, point to specific cellular processes to be used as therapeutic targets for further development. Along these lines, recent studies indicate that selecting genetically supported treatment targets doubles the success rate of both identifying clinically beneficial interventions and obtaining final approval by regulatory agencies. Because genetic variation contributes substantially to the risk, severity, outcome and recovery from stroke, a global collaboration of investigators established the International Stroke Genetics Consortium (ISGC) in order to discover and translate these genetic determinants. Rapid and barrier-free data access are essential to ensuring the fastest possible discovery process; consequently, the ISGC partnered with the American Heart Association Institute for Precision Cardiovascular Medicine to establish the Cerebrovascular Disease Knowledge Portal (CDKP), an open access platform to freely share stroke genomic data with the global research community.
Methods: The CDKP has been a joint effort between the ISGC, the Broad Institute, and the American Heart Association Institute for Precision Cardiovascular Medicine. Given its extensive experience with similar projects, the Broad Institute has developed the informatics tools utilized by the portal provides and currently hosts the data. A dedicated steering committee, consisting of ISGC members who contributed substantial amounts of data to the portal, will guide the future steps of the CDKP. All interested investigators and research organizations are encouraged to deposit stroke-related genomic data in the CDKP. Datasets are aggregated, integrated, and harmonized with one another to be used to their full potential. The CDKP has been built to house two types of data: summary data, consisting of summary statistics generated by published studies; and individual level data, consisting of full datasets that can be used to design and implement analyses from scratch. The CDKP will be publically available, but data visualization and query analyses will require registration as a user, allowing for activity to be logged and auditable.
Results: The CDKP offers three main tools: (1) an easy-to-use graphical user interphase (GUI) that allows the exploration of existing stroke genomics information; (2) a repository of full sets of summary statistics produced by landmark published studies in the field; and (3) a repository of individual level data, accessible through a secure informatic working space where investigators can access and analyze these data. The GUI offers a wide menu of integrated web-based tools for data visualization and analysis. These tools allow for queries of data that are broadly consented and sharable. There are a range

of queries that can be run on the portal allowing for a unique way to view and explore results through the (1) Integrative Genomics Viewer, (2) Minor Allele Frequencies Table, (3) Variant Finder. The CDKP can be accessed at: http://www.cerebrovascularportal.org/

Conclusion: Ultimately, the CDKP is working towards accommodating one of the ISGC's goals of liberal data sharing amongst collaborators and those interested in cerebrovascular disease. It will move to integrate into the AHA precision medicine platform to encourage further collaboration and allow for rapid discovery and translation of findings. Sharing of datasets across a portal will multiply the great effects that data sharing between collaborators has already produced. This is the precision medicine approach that the American Heart Association is fostering with the "Institution for Precision Cardiovascular Medicine", which the Cerebrovascular Disease Knowledge Portal will merge with to foster an open science environment for faster discovery and translation. By partnering with AHA Institute for Precision Cardiovascular Medicine to make the data as widely available as possible and to integrate tools for cutting edge data analysis, the Portal will to revolutionize how cardiovascular data can be discovered and utilized globally.



The CDKP homepage

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J. B. Crocker, M.D., Massachusetts General Physicians Organization (MGPO)

IMMERSE: Improving medication renewal management to reduce burden and improve care

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Introduction: Massachusetts General Hospital primary care and specialty care clinics process nearly 60,000 prescription renewal orders per month. The management of prescription renewals (Rx requests) is a daunting challenge for outpatient practices. (Sinski, 2012). Vetting renewal requests for safety and accuracy uses a significant amount of nursing, medical assistant, and physician time, and many groups lack standard medication renewal protocols. Many practices within integrated health care systems lack adequate support in personnel and IT tools to efficiently manage this task. (Schoenhaus et al, 2016; Guirguis-Blake, 2012). **Goals:** In response to these challenges, the Massachusetts General Physicians Organization designed **IMMERSE (*Integrated MGPO Medication Renewal Service),*** a centralized service to evaluate renewal requests against standard protocols and prepare them for approval by the provider or for further action by the practice. Through implementation of best practices and process standardization, IMMERSE aims to: 1) Decrease clinician burden 2) Increase process efficiency, 3) Reduce the risk of medication related errors, and 4) Improve the quality of care provided to patients.

Methods: ***Scope and Design*:** IMMERSE prepares medication renewal requests for 18 medication classes used to treat high prevalence chronic conditions (e.g., anti-hypertensives, cholesterol-lowering agents, thyroid medication, etc. Controlled medications are out of scope.) The work is completed using locally developed clinical algorithms with built-in population health and patient engagement measures. A central team of well-trained technicians works overnight, so that the majority of medication renewals and lab orders are batched and ready for review by the physician in the morning. Pertinent lab orders are teed up for authorization, and practice staff are notified of any related scheduling needs. ***Standard Process:*** The central team determines whether the request meets inclusion criteria based on drug class, then checks the request against a standard set of safety and accuracy criteria: **1**. **If the request passes**, IMMERSE prepares the Rx renewal and routes it to the physician, with a concise summary of the decision rules and clinical values used to evaluate the request. **2. If clinical parameters (e.g., blood pressure, LDL) are outside the allowable range**, an easy-to-recognize 'header' indicates that the physician needs to evaluate the information and decide how to proceed. **3. If the review fails the standard saftey and accuracy checks**, the reason for the failure is noted, and the Rx request is routed to the practice EHR refill pool (i.e., queue) for disposition by the practice staff.

Results: From pilot inception in October, 2016 through July 7, 2017, IMMERSE processed 16,630 prescription renewal requests for 65 physicians at 7 MGPO practices. A cross section of > 4,000 Rx renewal requests for 29 providers from 4

practices over a 1-month period was analyzed for protocol success and safety evaluation. A practice time savings analysis was also performed. **Based on this 1-month analysis: 65%** of Rx renewal requests were offloaded from RN/MA staff. **14%** of Rx renewal requests were duplicates, including ½ of all Rx renewal requests received by fax. **16%** (1 in 6) of Rx renewal requests triggered a safety concern, resulting in notification of the practice team, so that corrective action could be taken before the patient was exposed to risk. **An estimated 220-300 hours of RN/MA time (5-7 minutes per renewal) were returned to the practices** during the month. **An estimated 3.5 hours per month was returned to each physician** (3 minutes on average saved for each successfully processed Rx request).
Conclusion: Our findings highlight: 1) **the significant reduction of administrative burden for practice RN/MA's** 2) **the value of improved safety and patient re-engagement through the implementation of standardized refill management protocols** by a well trained central team, and 3) the benefit to local clinical operations of leveraging expertise across multiple domains (clinical, pharmacy, IT, operations, quality and safety) to achieve more efficient and effective outcomes.

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Susannah Daggett, Medicine - General Internal Medicine

"What I want and need to do": Understanding patients' goals for hip and knee osteoarthritis treatment

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Introduction: Hip and knee osteoarthritis are prevalent, disabling conditions with many treatment options, including total joint replacement surgery (TJR). Patients considering TJR must weigh the risks and benefits of surgery with those of nonsurgical treatment options, and take into account their own goals. For physicians who are partnering with patients in making this decision, it is helpful to understand the burden of disease and how it impacts patients' ability to do activities that are important to them. The goal of this study was to elicit these patient activity goals and examine them to better understand the impact of the disease on different populations.
Methods: This analysis is a preliminary exploration of patient-reported activity goals for hip and knee osteoarthritis treatment. Patients were asked an open-ended question, "What are 3 important activities that you want or need to do that you cannot do now due to your hip or knee?" and provided responses before a surgical consultation. Qualitative analysis was performed to analyze the responses and categorize them. The activity goals were compared by joint (hip vs. knee), gender, and age (≤64 vs. ≥65).
Results: 262/275 respondents provided one or more activity goals. Of these, 148 (56%) were female, 162 (62%) had knee as opposed to hip osteoarthritis, and the average age was 64.2 years old. The responses fell into 8 categories: walking, stairs, flexibility, activities of daily life, impact sports (such as running or basketball), moderate physical activity (such as swimming or dancing), social, and sleep. The most frequently listed goals were related to walking (70.6%), moderate physical activity (46.6%), and activities of daily life (37.0%). Walking without pain was the top listed goal across all groups. Knee patients were more likely to list stairs (35.8% knee vs. 15.0% hip). Male respondents were more likely to list impact sports (42.1% males vs. 29.7% for females), while females were more likely to list stairs (40.5% vs. 11.4% males). Older respondents were more likely to list walking (78.2% older vs. 61.7% younger), while younger respondents were more likely to list impact sports (46.7% vs. 25.4% older).
Conclusion: Patients with hip or knee osteoarthritis readily shared a range of activities that they wanted or needed to do but could not because of their condition. Improvement in walking was the most common desired activity goal. The provision of such information will assist surgeons in delivering patient-centered care and facilitating shared decision making conversations about potential treatments. Further research should explore how well treatments enable patients to achieve their individual goals.

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Adam Dalia, MD, MBA, Anesthesia, Critical Care and Pain Medicine

ECMO is a Team Sport: Institutional Survival Benefits of an ECMO Team

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Introduction: Extracorporeal membrane oxygenation has grown in popularity over the last decade with many institutions becoming referral centers for specialized care of these patients. At our institution prior to 2014 patients requiring care in the peri-ECMO period were treated by intensivists with specific training in ECMO but worked independently.

This isolated form of care was addressed in late 2013 with the formal initiation of an ECMO Team starting in 2014. The new multidisciplinary team established a set of protocols and guidelines to care for ECMO patients. The team addressed each phase of ECMO therapy from pre cannulation ECMO care, ECMO care, and post decannulation ECMO care. The formal ECMO team consisted of: cardiac surgery, cardiac anesthesia, intensivists, cardiology heart failure specialist, ICU nursing (NP/RN), perfusion services, respiratory therapy, nutrition, physical and occupational therapy, and an ethics committee member. Constant communication between all facets of the team throughout the peri-ECMO period facilitated safe care for these complex patients resulting in an improvement in survival to discharge.

Methods: All adult patients at our institution who required ECMO support between the years of 2009 and 2016 were retrospectively reviewed to identify key demographic and survival information. Manual chart review was conducted and survival to discharge was collected and separated into two groups, 2009-2013 and 2014-2016.

Results: There was a total of 265 patient charts reviewed who required ECMO support, 130 patients were placed on ECMO between June 2009- December 2013 and 135 patients between January 2014-December 2016. Survival to discharge for patients between 2009-2013 was 37.7% compared to a survival to discharge of 51.9% between 2014-2016 (P value = 0.02). Complete analysis located in Table 1.

Conclusion: The growth in utilization of ECMO at our institution triggered the need to form a structured multidisciplinary team for appropriate management of these complex patients. Prior to Jan 1, 2014 there was no concrete "ECMO Team", the patient was managed by individuals providing siloed care for these patients. After initiation and implementation of the "ECMO Team" a more collaborative approach to caring for these patients developed and outcomes seemed to reflect this benefit. Survival to discharge is an important marker to determine efficacy of a care team and patients who were cared for after 2014 by the ECMO Team showed improved survival compared to patients on ECMO who were treated at our institution prior to 2014. Further analysis of morbidity will need to be done to completely understand the true impact of this care team approach but the crude simplistic measurement of survival provides valuable insight into this team based care for ECMO patients.

	Total (n=265)	2009–2013 (n=130)	2014-2016 (n=135)	p-value
Age (years)	50.7 ± 14.9	52.8 ± 14.5	48.8 ± 15.1	0.03
ECMO duration (days)	9.3 ± 17.8	6.9 ± 11.6	11.8 ± 22.1	0.02
Mode of ECMO				<0.001
VA	165 (62.3)	99 (76.2)	66 (48.9)	
VV	67(25.3)	25 (19.2)	42 (31.1)	
Mixed	33 (12.45)	6 (4.6)	27 (20.0)	
Pre ECMO LV function	3.7± 1.4	3.9± 1.4	3.6± 1.4	0.23
Pre ECMO RV function	3.4± 1.4	3.2± 1.4	3.6± 1.4	0.03
Unit				<0.001
CSICU	143 (54.0)	49 (37.7)	94 (69.6)	
CCU	4 (1.5)	4 (3.1)	0 (0.0)	
MICU	43 (16.2)	9 (6.9)	34 (25.2)	
SICU	64 (24.2)	63 (48.5)	1 (0.7)	
Cath lab	4 (1.5)	3 (2.3)	1 (0.7)	
Multiple units	7 (2.6)	2 (1.5)	5 (3.7)	
Survived to discharge	116 (44.8)	49 (37.7)	67 (51.9)	0.02

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Sandra Danso-Bamfo, MBChB, MPH, Emergency

Assessment of a condom uterine balloon package for uncontrolled postpartum haemorrhage in Dar es Salaam, Tanzania: one year post implementation

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Introduction: Great strides have been made over the past 20 years in reducing the maternal mortality ratio in Tanzania. However, postpartum hemorrhage (PPH) remains the leading cause of maternal death, with considerable variability across the region. Over the past seven years, faculty from the Massachusetts General Hospital have developed a low cost uterine balloon tamponade package known as Every Second Matters-Uterine Balloon Tamponade (ESM-UBT) and have successfully implemented the package across various levels of health systems in South Sudan, Kenya, Sierra Leone, Senegal, Zambia,

Ghana, and Nepal. The aim of this study was to understand the impact ESM-UBT has had in Dar es Salaam, Tanzania one year subsequent to implementation; and to understand the barriers and facilitators to optimal use.
Methods: The ESM-UBT package was implemented across four teaching hospitals in Dar es Salaam in March 2016. Prospective data were collected on use of the ESM-UBT device between March 2016 and March 2017. Data on ESM-UBT device use were supplemented by structured interviews of skilled birth attendants at each of the study facilities. These interviews were audio recorded, transcribed and independently coded between May and July 2017.
Results: Ninety-five women received ESM-UBT devices between March 2016 and March 2017 among the four facilities. Ninety (94.7%) of the 95 had PPH from uterine atony. Of the 90 women with PPH from uterine atony, the ages ranged from 16-45 years (mean of 28.5 years ± 6.9). Eight of the 90 (8.9%) women underwent hysterectomy despite an ESM UBT device. Of these women, 87 (96.7%) survived. Forty-five (50%) of the 90 women with PPH from uterine atony had normal vital signs while 33 (36.7%) were in Class III shock and 12 (13.3%) were in Class IV shock. All (100%) 45 women who had normal vital signs or were in mild shock (45) and all women who were in Class III shock (33) survived. Seventy-five percent of the women in Class IV shock survived. Over 50 different providers inserted the device across the 4 facilities. Providers expressed overwhelming support for the implementation of the ESM-UBT device in their facilities and often mentioned that lower level facilities would stand to benefit from being trained in its use. The ESM-UBT device was reported easy to use. No patient-centric barriers to uptake were revealed.
Conclusion: The ESM-UBT device appears associated with high rates of survival especially when placed early in uncontrolled postpartum haemorrhage. There is widespread support for the use of the device across all cadres and sentiment that ESM-UBT implementation should expand.

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Sandra Danso-Bamfo, Medicine - General Internal Medicine

Student Facilitated MassHealth Registration at Nashua Street Jail

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Introduction: At any given time, 2.3 million people in the United States are held in correctional facilities, constituting the highest incarceration rate in the world[1]. Due to turnover in the jail system, a much larger number, nearly 12 million Americans, were detained in 2013 during court proceedings. The Nashua Street Jail (NSJ) houses nearly 600 male detainees engaged in court processes, who stay for a time ranging from several days to two years. The criminal justice-involved population has higher rates of chronic physical and mental health conditions than the general population[2]. Upon returning to their communities, many of these individuals lack health insurance and access to healthcare, as well as the social and financial resources to treat their conditions. In Massachusetts, many of these individuals are eligible for insurance through MassHealth (Commonwealth of Massachusetts' Medicaid and Children's Health Insurance Program). Increased insurance among individuals at discharge may help expand healthcare access, increase social stability, and lead to decreased rates of recidivism[1]. The student-faculty collaborative clinic at NSJ is part of The Crimson Care Collaborative (CCC), an inter-professional organization administered by the Stoeckle Center for Primary Care Innovation at Massachusetts General Hospital (MGH). Volunteers involved in the clinic are medical, nurse practitioner, physician assistant, dental, and undergraduate students from across Harvard Medical School, MGH Institute of Health Professions, Harvard School of Dental Medicine, and Harvard College. Student-faculty clinics are held at the jail once per week and include medical, mental health, education, dental, and MassHealth teams. The MassHealth initiative is a student led effort to enroll detainees scheduled for release into the MassHealth insurance program. The MassHealth initiative seeks to address barriers to healthcare for detainees during a particularly vulnerable period post-discharge, utilizing an interdisciplinary team-based approach. Enrollment in MassHealth while in jail could increase access to resources crucial to continued management of chronic health conditions and improved social stability post-discharge. The initiative provides student volunteers the opportunity to become more involved in advocacy and research. After a successful 3-month pilot, the focus of the MassHealth initiative has been robustness and sustainability.
Methods: Students on the MassHealth team complete online modules provided by the state of Massachusetts to become Certified Application Counsellors, as well as instructional training by the NSJ discharge planner. New student volunteers are on-boarded by current student volunteers on site during the weekly clinic. The jail's discharge planner individualizes resources for each detainee's transition back to the community, including health insurance enrollment. Based on upcoming court proceedings and prospective release date, the NSJ discharge planner identifies individuals at the jail who need MassHealth enrollment. A student will begin the enrollment process for typically 3 to 4 detainees during each clinic and pass-off the forms to the discharge planner to complete during normal work hours. Detainees may also register to vote at this time.

Results: Over the lifecycle of this initiative (i.e., 3-month pilot phase and subsequent 6-month rollout to date), our weekly clinic has initiated the MassHealth enrolment process for approximately 120 detainees. On average, 4 detainees have been enrolled per week. To date, 11 volunteers have been trained as Certified Application Counsellors (CAC) with an average of 2 attending each weekly clinic. Due to existing security protocols and staff limitations, detainees from different jail units cannot be seen in the clinic simultaneously, which limited our numbers to approximately 4 enrollments per session during the 3-month pilot. We developed a new workflow to overcome this logistical challenge (visiting detainees in their respective units) which increased our enrollment numbers to approximately 8 per session. Detainee-specific challenges include language barriers, low literacy, and vision problems.
Conclusion: The collaboration between CCC volunteers and NSJ staff to facilitate MassHealth enrollment appears to have resulted in successfully facilitating detainee enrolment in MassHealth and has been beneficial to both parties and has been well received by detainees. Several modifications to the enrolment process are being made to address the various challenges that were uncovered during the pilot phase. Transience of detainees in NSJ poses challenges in continuity of care and final MassHealth enrollment success. As such, follow-up of detainees to further explore the impact of insurance enrollment on overall health is warranted. Due to the somewhat lengthy process to complete MassHealth registration, that requires the detainee to be released, we have to-date been unable to track final outcomes. We will continue to recruit volunteers and work with NSJ to increase the number of people we can assist through this initiative and plan to ask volunteers to reflect on how this program has impacted their views about correctional health, health insurance provision, and health policy.

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Night Shift Work, *MTNR1B* Common Genetic Variant and Type 2 Diabetes: findings from the UK Biobank

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Introduction: Night shift work (NSW) has been associated with an increased risk of type 2 diabetes (T2D), possibly as a result of chronic misalignment between biological and social rhythms. *MTNR1B* T2D risk variant rs10830963 also has a strong adverse effect on insulin secretion. We investigaed whether NSW exacerbates the association between *MTNR1B* and T2D.
Methods: The UK Biobank is a prospective study in the UK. Work schedule was self-reported and T2D status was determined via self-report and ICD10 codes. Analysis included workers of European descent with genetic data and information on current [*n* =82,314; day workers (*ref*; n=68,050), shift work without NSW (n=6,976), sometimes NSW (n=4,094), usual NSW (n=1,100), and always NSW (n=2,084)] or lifetime (*n*= 18,256) work schedules. The association between *MTNR1B*, shift work and T2D (*n* =2,596) was examined using logistic regression, adjusted for age, sex, and ancestry. Interaction was tested using *MTNR1B* × shift work cross-product term.
Results: Each additional risk G allele (minor allele frequency =28%) was associated with 13% higher odds of T2D [OR(95% CI) =1.13(1.06-1.20)]. Any shift work was associated with higher odds of T2D [shift work without nights: 1.24 (1.08-1.42); sometimes NSW: 1.21 (1.02-1.44); usual NSW: 1.72 (1.30-2.28); and always NSW: 1.33 (1.06-1.67)]. Higher intensity of NSW (each additional average NSW per month) was also associated with 4% higher odds of T2D [1.04 (1.00-1.08)]. While current shift work did not exacerbate the association between *MTNR1B* and T2D [1.00 (0.94-1.08)], the effect of *MTNR1B* on odds of T2D was greatest in the highest intensity of NSW [>8 NSW/month; 2.36 (1.12-5.0)].
Conclusion: NSW intensity may exacerbate the relationship between *MTNR1B* risk variant and T2D in the UK Biobank. The Shift work, Heredity, Insulin resistance, and Food Timing (SHIFT) Study (NCT02997319) introduces high resolution assessment of shift work, diet and sleep and their effect on glucose metabolism to further elucidate this potential interaction.

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Use of angiotensin system inhibitors is associated with longer overall survival in newly diagnosed glioma patients and recurrent glioblastoma patients receiving chemotherapy and/or bevacizumab

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Introduction: Given prior studies that suggest the use of angiotensin system inhibitors (ASIs) is associated with prolonged overall survival (OS) and improved quality of life in glioblastoma (GBM) patients, we evaluated the effect of ASIs in glioma patients receiving chemotherapy and/or bevacizumab (BEV)[1].
Methods: Using retrospective data from newly diagnosed WHO grade 2-4 glioma patients from the Kaiser Permanente Tumor Registry of Northern California, we evaluated the impact of ASIs on OS by Cox proportional hazard model analysis for subgroups who received cytotoxic therapy, cytotoxic therapy with BEV, or BEV alone, as well as in a separate cohort of recurrent GBM (rGBM) patients receiving low- or standard-dose BEV.
Results: Of the 1186 glioma patients who received chemotherapy, ASI exposure significantly improved OS (HR=0.82; 95%CI=0.71, 0.93; p=0.003). When stratified by BEV exposure, a sub-analysis revealed further OS advantage for the BEV group (HR=0.75, 95%CI=0.62, 0.90; p=0.002). In a second cohort of 181 rGBM patients who received BEV in varying dosages, ASI exposure conferred an OS advantage (HR=0.649; 95%CI=0.46, 0.92; p=0.016). Moreover, patients who received low-dose BEV treatment with ASI exposure had a significantly longer OS (median=99 weeks; 95%CI=44.3, 205) than those without ASI (median OS=55.6 weeks; 95%CI=37.7-73.7; p=0.032).
Conclusion: ASI use is associated with longer OS in glioma patients. Further survival advantage with ASI use was observed in rGBM patients receiving low-dose bevacizumab. These data warrant prospective evaluation of adding ASIs to low-dose BEV treatment in GBM patients to improve the efficacy of standard therapies. [1]Levin, V.A., Chan, J., Datta, M., Yee, J.L., and Jain, R.K. "Effect of angiotensin system inhibitors on survival in newly diagnosed glioma patients and recurrent glioblastoma patients receiving chemotherapy and/or bevacizumab," J Neurooncol (2017) doi:10.1007/s11060-017-2528-3 (available online ahead of print).

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Eliza J. Davidson, B.S., Psychiatry

Effect of internal versus external focus of attention on negative cognitions and anxiety in Body Dysmorphic Disorder and Social Anxiety Disorder

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Introduction: Self-focused attention is an awareness of self-referent, internally-focused, thoughts, feelings, beliefs, and sensations. Heightened self-focused attention is associated with many psychiatric disorders, such as Social Anxiety Disorder (SAD) and Body Dysmorphic Disorder (BDD), and represents a potential transdiagnostic target for treatment. Individuals with SAD focus attention inward when triggered by stressful social situations. In BDD, self-focused attention may be triggered by looking in a mirror or being in social situations. Internal attention toward negative thoughts may elicit greater preoccupation with perceived defects in appearance, and preclude the processing of alternative, corrective information from the environment. This study examined the effect of an internal versus external focus of attention on negative cognitions and overall anxiety during social interactions. We hypothesized that participants with SAD and BDD would demonstrate reductions in negative cognitions and overall anxiety during the external focus of attention condition relative to the internal focus of attention condition, and that these reductions would be greater than in healthy control participants (HC).
Methods: Participants were 4 clinical patients (2 with primary BDD, 2 with primary SAD) and 3 HC. Participants were screened for eligibility using the SCID-I/P and disorder specific symptom severity measures (BDD-Y-BOCS for BDD participants, and Liebowitz Social Anxiety Scale (LSAS) for SAD participants). Healthy volunteers did not meet criteria for any lifetime diagnosis of an Axis I disorder. Participants completed the Self-Focused Attention (SFA) measure to assess trait level self-focused attention. Participants were then instructed to use inward or outward attention instructions in two role plays involving meeting and speaking with an unfamiliar confederate for 4 minutes. To examine the effect of attention instructions on subjective anxiety levels, participants completed the State Trait Anxiety Inventory (STAI) and Brief Fear of Negative Evaluation Scale (BFNE) before and after each role play. After each role play, participants also completed the Social Interaction Self-Statement Test (SISST) to assess the effect of attention on self-referent cognitions. The Focus of Attention Questionnaire (FAQ) was completed as a check that our manipulation of attention instructions was successful. Given the

small sample sizes in each group, statistical tests of significance would be underpowered. Therefore, we employed visual inspection of means and standard deviations to examine our hypotheses.
Results: Clinical participants scored moderate (LSAS: M=79.00, SD=2.83) to severe (BDD-Y-BOCS: M=30.00, SD=4.24) on symptom severity measures. BDD participants demonstrated elevated trait SFA scores (M=13.00, SD=7.07) compared to HC (M=6.33, SD=3.51), however, not as elevated as SAD participants (M=20.50, SD=4.95). Individuals with BDD (M=47.50, SD=10.60) and SAD (M=46.00, SD=1.41) scored comparably on baseline BFNE, well above HC (M=26.00, SD=6.55). The outward manipulation was successful for HC and BDD subjects, but not for the two SAD participants, and the inward manipulation was successful, except for 1 HC and 1 SAD patient. Nevertheless, all BDD and SAD patients showed greater reductions in STAI scores in the outward attention condition (STAI BDD M diff=.20, SD=.28; STAI SAD M diff=.20, SD=.00) versus the inward attention condition (STAI BDD M diff=.05, SD=.07; STAI SAD M diff=-.13, SD=.60) relative to HC (outward STAI HC M diff=.08, SD=.14, inward STAI HC M diff=-.02, SD=.08). As expected, BDD participants had lower SISST scores in the outward (M=15.50, SD =.71) versus inward (M=24.00, SD =1.41) attention conditions, as compared to HC (outward: M=12.33, SD=4.04; inward: M=12.00, SD=2.65), for whom an outward attention instruction did not impact negative cognitions on the SISST.
Conclusion: Our results support cognitive models of BDD and SAD, which propose that such patients have elevated levels of self-focused attention and fear of negative evaluation in social contexts. An outward attentional instruction can result in a decrease of negative cognitions; however, individuals with SAD may require more training in adopting this attentional focus. Future research should examine explicit attention training as a potential transdiagnostic target for treatment.

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Point-of-Care Virtual Radiology Consultations in Primary Care: a New Model for Patient-Centered Care in Radiology

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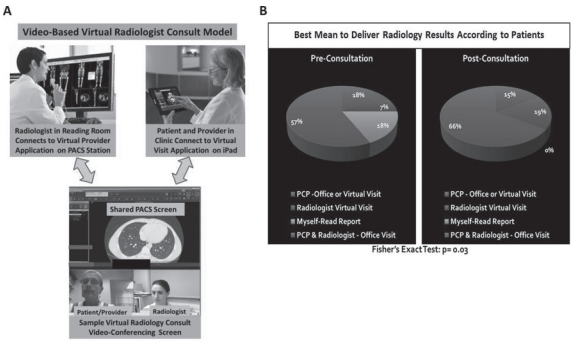
Introduction: The use of virtual visits for routine outpatient care delivery has been steadily increasing. Limited data are available on the role of such visits in radiology. The goal of this study is to assess the value of point-of-care virtual consultations in radiology, through the implementation of synchronous video-based virtual consultations whereby referring primary care physicians can consult with a radiologist virtually and review studies in real-time while seeing a patient.
Methods: We conducted an IRB-approved feasibility study of video-based radiology consultations in an internal medicine primary care clinic at a tertiary academic medical center. The study included 3 primary care providers (PCP) and enrolled 40 patients. Inclusion criteria consisted of the following: age >18, English-speaking, recent radiology exam at MGH, and patients indicating verbal consent. Patients completed a pre- and post-visit survey. PCPs completed a post-visit survey. Primary study endpoints included the effect on patient and provider satisfaction, effect on patient experience and understanding of medical condition, and impact on PCP's management decisions. Statistical significance was assessed using student's t-test and Fisher's exact test.
Results: Both patients and primary care providers indicated high satisfaction with the virtual radiology consult experience on a likert scale (92 and 96% respectively). 89% of the patients reported increased understanding of their disease and improved patient experience as a result of the radiologist virtual visits. 83% of PCPs indicated that the consult was helpful for their management decisions. Virtual visits increased patient interest in receiving their imaging results from radiologists; 56% indicated interest in the pre-visit survey versus 88% in the post-visit survey (p=0.03).
Conclusion: Initial experience with virtual radiology consults show high rates of patient and provider satisfaction and increasing demand for the availability of these visits. Virtual radiology consults have the potential to advance radiology's value in care delivery by allowing more clinically-relevant and personalized radiology care and by promoting patient-centered practice models.



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Adriana De Julio, MD, Psychiatry

Analyzing Co-morbid Conditions in the Neuropsychiatric Syndrome of Tinnitus

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Introduction: Tinnitus is the sensation of hearing a sound with no external auditory stimulus present. It is a public health issue correlated with noise exposure, military service, traumatic brain injury, small vessel disease, smoking, stress, and socio-economic status. Clinical experience and a recent literature review point at tinnitus as a neuropsychiatric condition involving both auditory and non-auditory cortical areas of the brain and affecting brain auditory circuitry. The aim of our study was to evaluate the correlation between tinnitus and comorbidities measured using common survey instruments that quantify tinnitus, cognitive functioning, depression, and anxiety. Retrospective chart review for 400 adults seen in the Comprehensive Tinnitus Clinic at Massachusetts General Hospital from 2011- 2016 was undertaken. Demographics, analysis of a 6 page questionnaire regarding symptoms of tinnitus, medical history, neurological exam, and Tinnitus Handicap Inventory (THI) scores were analyzed. In most charts Montreal Cognitive Assessment, Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) were also available. We attempt to explain the correlation between medical comorbidities and complaints of tinnitus such as attention difficulties, frontal lobe executive dysfunction, anxiety, depression, hearing loss and obstructive sleep apnea. Tinnitus remains a challenging condition to evaluate and treat. We approached each clinic patient using a three prong framework to understand tinnitus and treat it as a neuropsychiatric syndrome.

Methods: A retrospective chart review was performed on chart of 400 patients who received treatment and evaluation in the Comprehensive Tinnitus Clinic for tinnitus as a part of the clinical collaboration between Massachusetts Eye and Ear and Massachusetts General Hospital between 2011 and 2016. Only patients with reported tinnitus who had completed at Tinnitus Handicap Inventory (THI) and Beck Depression Inventory (BDI) data were analyzed. Their demographics including age, ethnicity, race, sex, marital status, education level, and employment status were collected. Using EQIP we confirmed ICD-10 and ICD-9 diagnosis codes for tinnitus, depression, anxiety, obstructive sleep apnea, insomnia, and sleep disorder. All data was analyzed using R software. Normal distribution of continuous variables was verified according to the comparison of mean and median, and the Pearson (omnibus K2) test. Correlation coefficients were calculated to evaluate the relationship between tinnitus symptom intensity and baseline severity of depression during the initial interview. Pearson correlation coefficients were used in all cases to neuropsychiatric variables that have previously been correlated significantly with tinnitus including: obstructive sleep apnea, insomnia, snoring depression, anxiety, illicit substance abuse, and suicidal ideation. For the regression model, data transformations and polynomial models were used to test the best fit, model assumptions were tested by analyses of residuals, and influence diagnostics were conducted using Cook's distance. Unless otherwise noted, group data are presented in the text as mean±standard error (SE[ZC1]).

Results: Out of 200 chart 50 were excluded as they did not have a THI score or their were insufficient details to justify a diagnosis of tinnitus. A total of 150 patients charts to date have been analyzed that fulfilled the study criteria. Each patient participated in the clinical interview, exam, and completed an extensive health questionnaire with a complete review of systems. The demographic characteristics of the clinic cases analyzed are shown in **Table 1**. The clinic has been evaluating men and women equally. An older population is being evaluated with the average age being 59 and a SD +/-12. The age range was between 28-96 years old. Ethnically 92% of patients identified as Caucasian, 2% as Hispanic and 2% as Asian. 30% of patient have a Master's degree or higher. Over 60% have gainful employment or are retired; a minority were unemployed or disabled. The length of time of tinnitus symptoms and how that might correlate with depression and anxiety was analyzed and characteristics are shown in **Table 2**. The prevalence of anxiety was higher among patients with intermittent tinnitus

relative to those with persistent tinnitus (55% v. 27%). Anxiety and depression were equally prevalent amongst those with persistent tinnitus (30% and 27% respectively). Patient who had experienced symptoms for over 10 years were more likely to have depression compared to those with intermittent tinnitus (41% v. 25%). Analysis with t-test and regression modeling using Pearson's revealed negative effects of the THI score on BDI and BAI scores. We found that moderate to severe scores on THI correlate directly with BDI and BAI scores as shown in **Table 3**. Catastrophic cases accounted for ~2% of patient's we evaluated and were highly correlated with suicidality (Table 3) and addiction.
Conclusion: A neuropsychiatric circuitry approach should be relied on to lead the way in advancing the understanding of the syndrome of tinnitus in order to continue research on therapeutic breakthroughs for symptom relief.

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Melissa de Leon, Psychiatry

Buspirone for the Treatment of Anxiety Disorders in Patients with High-Functioning Autism Spectrum Disorder: A Retrospective Chart Review

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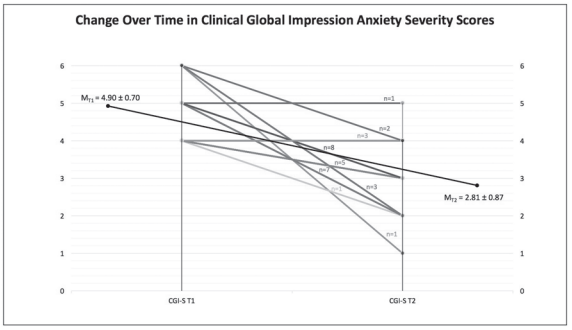
Introduction: Anxiety disorders commonly develop and may intensify in severity over the course of ASD. Buspirone is a commonly prescribed anxiolytic drug with a favorable tolerability profile and may offer potential benefits in anxiety management for patients with ASD. Tolerability and efficacy of buspirone in treating anxiety disorders comorbid with ASD remain to be explored.
Methods: Data from patients, ages 8-17, diagnosed with ASD and anxiety disorders who received buspirone treatment was analyzed via retrospective chart review over a yearlong timespan (n=31). Demographic information, treatment data and adverse events were recorded. Efficacy was assessed via the Clinical Global Impression Scale (CGI) severity and improvement scores noted by each treating clinician.
Results: A total of 31 patients received at least one dose of buspirone during the determined period, with an average dose of 41.61±24.10 milligrams for an average duration of 272±125 days. The average CGI-S scores (M_{T1}=4.90±0.70; M_{T2}=2.81±0.87) revealed an overall improvement in severity of anxiety symptoms. Overall, 29% of patients attained mild improvement (CGI-I=3) and 58% of patients showed significant improvement in anxiety symptoms (CGI-I≤2). Two patients developed a treatment emergent adverse event (activation and mood lability). There were no other adverse events present for any of the remaining 29 patients.
Conclusion: Buspirone may improve anxiety disorders comorbid with ASD, and is mostly well tolerated. Further research with prospective and randomized controlled trials is necessary.

Demographic and Clinical Characteristics

Demographic Characteristics		
Participants (total)		*31*
Gender (men)		*25 (81%)*
Age (years)	*Mean±SD*	*13±3*
	Range	*8-17*
Clinical Characteristics		
Baseline Anxiety Severity (CGI-S score)		*4.90±0.70*
Diagnoses (DSM-V)		
ASD		*30 (97%)*
ADHD		*27 (87%)*
Mood Disorders		*22 (71%)*
Anxiety Disorders		*21 (68%)*
Other		*5 (16%)*



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Emily de Redon, BA, Medicine

Evaluating the Impact of a Blood Pressure Remote Telemonitoring Program (BP Connect)

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Introduction: The prevalence of hypertension is around 30 – 45% among the general population. Hypertension contributes to 1 out of 7 deaths in the United States and approximately 70% of persons who have a first heart attack or stroke. Timely treatment and optimal management of hypertension is associated with substantial reductions in stroke incidence (35%–40%), myocardial infarction (20%–25%), and heart failure (>50%). Additionally, remote monitoring with active intervention by medical professionals (telemonitoring) improves drug compliance and increase the target blood pressure (BP) achievement rate. BP Connect is a remote monitoring program to augment care and disease self-management in hypertensive patients. The program aims to engage patients in self-care by providing a secure web-based platform to record and track their BP. In addition, care providers can view the uploaded data, thereby, ensuring the continuum of care beyond the hospital setting.
Methods: A total of 288 adult patients diagnosed with hypertension (baseline blood pressure of ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic) were recruited from primary care and specialty clinics within the Partners Healthcare network of hospitals (Faulkner, Renal, Endocrinology and Cardiology departments at Brigham and Women's Hospital and Massachusetts General Hospitals Women's Health Association). The primary outcome was the impact of BP Connect on blood pressure as measured by the change in the proportion of patients with controlled BP (ie, <140/90 mm Hg) from the initial visit to the 3-month clinic visit. Secondary outcomes included the change in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at close-out.
Results: Among the 149 patients from primary care clinics who completed the program to-date 48.0 % of patients had uncontrolled BP (>140/90 mm Hg) vs 64.0 % at baseline (P= 0.01). At 3 months, there was a significant decline in the mean SBP (-10.1, P= <0.01) and the mean DBP (-4.3, P= <0.01). Among the 139 patients from specialty clinics who completed this program, BP was controlled at 3 months in 43.2% of patients compared with 11.2 % patients at baseline (P= 0.001). A significant decrease in the mean SBP (-5.2, P <0.00) and in the mean DBP (-2.5, P= 0.01) were also noted.
Conclusion: Overall, the BP Connect program shows potential to improve clinical outcomes in hypertensive patients. The program provides an opportunity for participants to track their BP measurements on a web platform to foster patient participation in their own disease management that may improve patient outcomes and decrease burden on the care providers.

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Sandy Deden, Massachusetts General Physicians Organization (MGPO)

The Evolution of Physician Communications

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Introduction: With the formation of the Massachusetts Physicians Organization (MGPO) in 1994, it became clear early on that communication to the physicians would be essential. That year the *Fruit Street Physician* was created, a 4-page monthly, printed black-and-white newsletter to keep the more than 800 MGH physicians updated on payer contracts, managed care information, and the MGPO's activities and finances. Fast forward to 2017, and while the *Fruit Street Physician* monthly newsletter still keeps the more than 2,900 physicians informed about important MGH/MGPO projects, initiatives, and priorities for physicians, the communications portfolio has evolved.
Methods: Methods Here are the channels that the MGPO currently uses to communicate to its physicians, a strategic combination of content and technology: -- Both a print and online version of the *Fruit Street Physician* -- A well-designed intranet which describes MGPO programs and departments, as well as personal results of the twice-yearly Quality Incentive Program, the MGPO Physician Survey data, and other information. -- Emails branded by program to help target messages -- A YouTube channel featuring a popular short video series, *Two Things,* where physicians talk about important initiatives: https://www.youtube.com/user/MGPOOnline -- A Twitter account with more than 800 followers which promotes the published papers and awards of MGPO physicians and tweets content for MGPO physicians at @MassGeneralMDs -- Monthly lunches with the MGPO leadership -- Interdepartmental meet and greet gatherings
Results: We've gone from only having anecdotal information about how many physicians read the print version of the *Fruit Street Physician*, to having a full dashboard where we can track engagement analytics on all of our channels: -- How many people open our emails -- How many people view the videos -- Traffic to our intranet site and what they read there -- The

topics physicians are interested in This has helped the communications team go beyond just giving information we think the MGPO physicians should know. Using data and information from informal, in-person events, we can communicate more efficiently and more responsively, help reduce administrative burden, reach more physicians with social media, support the overall MGPO goals, and get better feedback from our audience. For example, a recent poll of physicians revealed that they wanted more training to optimize their use of Partners *e*Care (Epic). We added the training to the MGPO Quality Incentive Program, created a badge card of available Epic help resources, and pushed that information through all our channels, increasing the reach of the message.
Conclusion: While it can be difficult being a small communications team in a large health care environment where the information stream is constant, we have learned to use a strategic combination of word economy, focused content, data, and technology to provide high-quality comunications to physicians and promote their engagement with the MGPO.

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Sophie Desmonde, PhD, Medicine - General Internal Medicine

Cost-effectiveness of pre-emptive switch to efavirenz (EFV) in HIV-infected children

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Introduction: Pre-emptive switching to EFV for HIV-infected children suppressed on lopinavir/ritonavir (LPV/r) can simplify ART while preserving LPV/r for second-line treatment. The South African NEVEREST3 trial found this switch strategy to be non-inferior to remaining on LPV/r. The MONOD ANRS 12206 trial in Côte d'Ivoire showed similar 6-month outcomes, although limited by low event rates. We evaluated the cost-effectiveness of a preemptive switch to EFV.
Methods: We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)-Pediatric model to simulate South African children suppressed on LPV/r. The base case used NEVEREST3 data to examine 3 strategies: 1) Switch: switch to EFV-based ART (initial 24-week RNA suppression [<1000c/ml]: 98%; virologic failure (VF) after 24-week suppression: 0.15%/month), followed by return to 2nd-line LPV/r at observed VF; 2) WHO guidelines: Remain on LPV/r (VF after initial suppression: 0.22%/month), with switch to 2nd-line NNRTIs at observed VF; and 3) LPV/r only: Remain on LPV/r (VF after initial suppression: 0.22%/month) with no 2nd-line regimen, reflecting practice in many settings. We projected life expectancy (LE) and HIV-related healthcare costs. Sensitivity analyses varied all key clinical and cost parameters. A secondary analysis used data from MONOD, which also reported EFV 24-week suppression of 98%, but higher monthly VF after initial suppression for EFV (0.72%) than for LPV/r (0.34%).
Results: With NEVEREST3 data, the switch strategy led to the longest projected LE (21.38y) and lowest projected lifetime cost ($32,720; Table). Results were not affected by plausible variations in ART or healthcare costs, loss to follow-up rates, or age at time of LPV/r initiation or ART switch (unless this affected virologic outcomes on ART). Results were modestly sensitive to initial suppression rates: if 24 week RNA<1000c/ml was <90% for children switching to EFV, WHO guidelines was preferred. Results were most sensitive to risk of VF after initial suppression. This risk for children switching to EFV needed to be equal to or lower than that for children remaining on LPV/r for the switch strategy to remain the most effective and cost-saving. With MONOD data, for example, the WHO guidelines strategy maximized LE (20.21y) and minimized cost ($33,570; Table).
Conclusion: For children similar to NEVEREST3 participants and suppressed on LPV/r-based ART, pre-emptive switching to EFV can improve clinical outcomes and be cost-saving.

Model-projected results

	Model-projected results		
	Life expectancy (years, discounted)	Lifetime costs (USD, discounted)	Cost-effectiveness
South African children suppressed on LPV/r (NEVEREST3 data)			
Switch to EFV	21.38	32,720	--
Stay on LPV/r with 2nd line ART (WHO guidelines)	21.12	34,230	More expensive, less effective
Stay on LPV/r, no 2nd line ART (LPV/r only)	20.11	46,140	More expensive, less effective
South African children suppressed on LPV/r (MONOD data)			
Stay on LPV/r with 2nd line ART (WHO guidelines)	20.21	33,570	--
Switch to EFV	19.68	37,333	More expensive, less effective
Stay on LPV/r, no 2nd line ART (LPV/r only)	19.03	44,259	More expensive, less effective

* Strategies listed in order of ascending costs.

USD: United States dollars; LPV/r: lopinavir/ritonavir; ART: antiretroviral therapy; EFV: efavirenz; WHO: World Health Organization.

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Laura E. Dichtel, MD, MHS, Medicine - Endocrine-Neuroendocrine

Plasma Free Cortisol vs. Total Cortisol in Healthy Individuals and in States of High and Low Cortisol Binding Globulin, Including Oral Contraceptive Use, Cirrhosis and Critical Illness: Implications for Diagnosing Adrenal Insufficiency

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Introduction: Accurate diagnosis of adrenal insufficiency (AI) is critical, as there are risks to both over and under diagnosis. Data using LC-MS/MS assays for total cortisol (TC) and free cortisol (FC) in states of high or low cortisol binding globulin (CBG) levels, including oral estrogen use, cirrhosis and critical illness, are needed. The goals of this study were to determine: 1) the relationship between TC and FC levels in healthy individuals and groups with abnormal CBG levels, and 2) the FC level by LC-MS/MS that best predicts a TC of 18 μg/dl (the standard AI diagnostic cut-off on ACTH-stimulation testing) in healthy individuals.

Methods: 338 subjects in 4 groups were studied: healthy controls (HC)(n=243), oral contraceptive users (OCP)(n=31), patients with cirrhosis (n=38) and intensive care unit patients (ICU)(n=26). FC and TC were measured by LC-MS/MS and albumin by spectrophotometry (Quest Diagnostics Nichols Institute, San Juan Capistrano, CA), and CBG by ELISA (Biovendor, Ashville, NC).

Results: Mean age was 48±17 y and mean BMI 28±7 kg/m^2. Mean albumin (g/dL) and CBG (μg/mL) were higher in OCP and HC than in cirrhosis and ICU [(albumin: OCP 4.6±0.3, HC 4.7±0.3 versus cirrhosis 3.5±0.9 and ICU 3.1±0.7, $p<0.001$) and (CBG: OCP 57±18 and HC 28±7 versus ICU 22±4 and cirrhosis 21±7, $p<0.0001$)] (Figure 1 A-D). CBG correlated weakly with albumin in HC ($R=0.32$, $p<0.0001$) and cirrhosis ($R=0.46$, $p<0.02$) but not in OCP or ICU (Figure 1 E-F). Mean random TC (μg/dL) was 18.9±8.5 in OCP, 14.7±6.6 in ICU, 11.5±7.3 in HC and 9.9±5.7 in cirrhosis (Figure 2 A,C). Mean FC (μg/dL) and % FC were highest in ICU subjects (FC: ICU 1.29±1.08, cirrhosis 0.59±0.47, HC 0.58±0.67 and OCP 0.33±0.15, $p<0.01$ vs. ICU; % FC: ICU 7.7±4.8%, cirrhosis 5.4±2.7%, HC 4.2±2.2% and OCP 1.8±0.8%, $p<0.05$ vs. ICU)(Figure 2 B,D). TC strongly correlated with FC in the ICU, HC and cirrhosis groups and more weakly in the OCP group (ICU $R=0.91$, HC $R=0.90$, cirrhosis $R=0.86$, OCP $R=0.70$, all $p<0.0001$)(Figure 2 E). Consistent with Hamrahian *et al*, ICU subjects with albumin <2.5 gm/dL had higher FC despite similar TC. In receiver operator curve (ROC) analysis in the HC group, an FC cutoff of 1.0 μg/dL predicted a TC of ≥18 μg/dL with 91% sensitivity and 98% specificity (AUC 0.98, $p<0.0001$). No HC subject with an FC ≥ 1.6 μg/dL had a TC < 18 μg/dL (67% sensitivity; 100% specificity). An FC cutoff of ≥1.0 μg/dL predicted a TC of ≥15.1 mcg/dL in ICU and ≥13.4 mcg/dL in cirrhosis with 100% sensitivity but only 92% and 83% specificity, respectively. In a separate group of 8 HC who underwent ACTH-stimulation testing, all had stimulated TC ≥ 18 μg/dL and FC levels ≥1.0 μg/dL, except one, who had a TC of 16.7 μg/dL with an FC of 1.4 μg/dl.

Conclusion: An FC of ≥ 1.0 μg/dL in this LC-MS/MS assay predicts a TC level of ≥ 18 μg/dL with maximum sensitivity and specificity. Clinicians should use caution in interpreting TC levels in patient groups with altered CBG levels, particularly in women on OCPs, given the variable resulting increase in CBG.

Table 1. Subject Characteristics and Laboratory Values

	Healthy Controls (n = 243)	OCP (n = 31)	Cirrhosis (n = 38)	ICU (n = 26)
Subject Demographics				
Age (years)	47 ± 16^{A}	30 ± 8^{B}	56 ± 12^{C}	60 ± 16^{C}
Sex (% female)	130 (53%)	31 (100%)	12 (32%)	12 (46%)
BMI (kg/m^2)	27.9 ± 5.9^{AB}	24.9 ± 3.6^{B}	29.6 ± 8.3^{A}	30.2 ± 10.5^{A}
Caucasian (n,%)	170 (70%)	25 (81%)	28 (74%)	21 (81%)
Outpatient (n,%)	141 (58%)	27 (87%)	24 (63%)	N/A
ER Visit (n,%)	102 (42%)	4 (13%)		N/A
Inpatient (n,%)	N/A	N/A	14 (37%)	26 (100%)
Laboratory Values*				
Total Protein (g/dL)	7.1 ± 0.3^{A}	6.8 ± 0.4^{AB}	6.8 ± 0.9^{A}	5.9 ± 0.9^{B}
Total Bili (mg/dL)	0.6 ± 0.8^{A}	0.3 ± 0.1^{A}	4.3 ± 7.1^{B}	0.7 ± 0.8^{A}
AST (U/L)	32 ± 4^{A}	24 ± 13^{A}	81 ± 63^{B}	61 ± 61^{B}
ALT (U/L)	30 ± 57^{A}	19 ± 10^{A}	43 ± 33^{B}	52 ± 54^{AB}
Sodium (mmol/L)	141 ± 3^{AB}	142 ± 3^{AB}	138 ± 7^{B}	140 ± 4^{A}
Creatinine (mg/dL)	0.86 ± 0.20^{AB}	0.77 ± 0.20^{AB}	0.83 ± 0.70^{A}	1.27 ± 1.10^{B}
INR			1.3 ± 0.3	1.2 ± 0.3
Disease Specific Risk Scores				
MELD Score			8.2 ± 1.0	
SOFA Score				6.2 ± 3.1
Cortisol & Binding Globulin Data				
Albumin (g/dL)	4.7 ± 0.3^{A}	4.6 ± 0.3^{A}	3.5 ± 0.9^{B}	3.1 ± 0.7^{C}
CBG (µg/mL)	28 ± 7^{A}	57 ± 18^{B}	21 ± 7^{C}	22 ± 4^{C}
Total Cortisol (µg/dL)	11.5 ± 7.3^{A}	18.9 ± 8.5^{B}	9.9 ± 5.7^{A}	14.7 ± 6.6^{AB}
Free Cortisol (µg/dL)	0.58 ± 0.67^{A}	0.33 ± 0.15^{A}	0.59 ± 0.47^{A}	1.29 ± 1.08^{B}
Percent Free Cortisol (%)	4.2 ± 2.2^{A}	1.8 ± 0.8^{B}	5.4 ± 2.7^{A}	7.7 ± 4.8^{C}

Table 1: Values NOT connected by the same letter indicate a significant difference (p<0.05). Note: * indicates subset of Healthy Controls and OCPs as follows: Total Protein: HC n=38, OCP=17; Total Bilirubin: HC=134, OCP=10; AST and ALT: HC=139; Na and Cr: OCP=12; Na HC=214, OCP=21. Abbreviations: MELD=Model for End-Stage Liver Disease, SOFA=Sequential Organ Failure Assessment, INR=international normalized ratio.

Table 1

Figure 1: Albumin and CBG

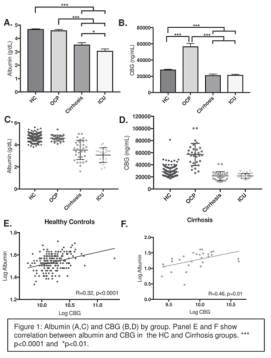

Figure 1: Albumin (A,C) and CBG (B,D) by group. Panel E and F show correlation between albumin and CBG in the HC and Cirrhosis groups. *** p<0.0001 and *p<0.01.

Figure 2: Total and Free Cortisol by Group

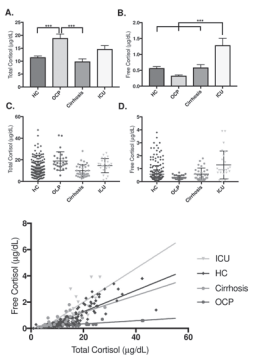

Figure 2: Total cortisol (A,C) and free cortisol (B,D) by group. ***p<0.0001 and *p<0.01. (E) Correlation between free and total cortisol by group on the same axis for comparison with p<0.0001 for all correlations and R values as follows: HC R=0.80, OCP R=0.70, Cirrhosis R=0.86 and OCP R=0.91. Unlogged correlations shown with R and p-values reported for analysis after log transformation.

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Jacob G. Dinerman, BA, Psychiatry

Efficacy of Lithium and Quetiapine in Adolescents and Young Adults with Bipolar Disorder

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Introduction: Quetiapine (QTP) is a second generation anti-psychotic approved for bipolar disorder, but its efficacy in adolescents and young adults with bipolar depression is mixed. Randomized trials of bipolar adolescent and young adults on QTP found that in some studies QTP was statistically significantly better than placebo, while in others, it was not. The present study reanalyzed data from a randomized comparative effectiveness trial of QTP and lithium (Li) to examine differential effects among adolescents and young adults with bipolar disorder, hypothesizing that Li would demonstrate a stronger effect, given the inconsistent results of QTP.

Methods: Adult outpatients with bipolar disorder (N=482) were randomized to QTP plus personalized adjunctive treatment or Li plus personalized adjunctive treatment for 24 weeks. For this analysis, we only included participants between the ages of 18 and 25 who met criteria for a depressive episode at baseline. Clinical outcomes analyzed in the present study included the Clinical Global Impressions Scale—Bipolar Version (CGI-BP), the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), and the Range of Impaired Functioning Tool (LIFE-RIFT). Analysis of covariance (ANCOVA) was used to test change between groups over time on each scale, controlling for symptom severity at intake as well as age of onset to examine possible moderating effects.

Results: There were 54 participants included in this analysis. Participants in this sample were majority female (n=36) with a mean age of 22.4 (*SD*=2.01). No differences were found between those randomized to QTP (n=29) and those randomized to Li (n=25) in regards to age, gender, or other demographic variables (p>0.05). ANCOVAs demonstrated significant improvement on the CGI-BP both for mania (delta=-0.9; F=5.85; p=0.005) and depression (delta=-2.26; F= 3.63; p=0.035) by the end of treatment, controlling for initial symptom severity and randomization group. Similar improvement was found on the LIFE-RIFT (delta=-5.30; F=6.85; p=0.003), but not on the Q-LES-Q (delta=12.53; F=2.84; p=0.070) from pre- to post-treatment. These findings did not vary between treatment conditions (p>0.05).

Conclusion: We found that adolescents and young adults experience significant improvement when taking Li, but not more than those taking QTP. While significant improvements in quality of life were not observed with the use of Li or QTP, these data indicate that both treatments decrease bipolar symptoms and functional impairment in adolescents and young adults with bipolar depression. These findings are limited by a small sample size. Future research should evaluate whether this trend holds true across other second generation anti-psychotics in adolescent and young adults populations.

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Gabrielle Donahue, B.A., Orthopedics

Obesity is Not Associated with Hip Failure in Patinets with Articular Surface Replacement of the Hip

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Introduction: In patients with metal-on-metal (MoM) hip articulations, metal wear and corrosion can emanate from the prosthesis and have been associated with adverse local tissue reaction (ALTR) in these patients. It has been hypothesized that patients with higher BMI will have increased edge loading, which may contribute to higher metal ion levels. The effect of obesity on the failure of MoM hip resurfacing and THA remains unclear in the literature. The primary aim of this study was to investigate whether obese patients (≥30 kg/m^2 BMI) were at increased risk of elevated blood metal ion levels if they were treated with the Articular Surface Replacement (ASR) Hip System (DePuy Orthopaedics, Warsaw, IN, USA). The secondary aim of this study sought to investigate if obesity was associated with a higher prevalence of ALTR.

Methods: The study cohort consisted of 360 patients who underwent hip arthroplasty with either ASR resurfacing arthroplasty (HRA) or total hip arthroplasty (THA), enrolled in a prospective, multicenter study following the voluntary recall of this system. All patients had a valid anteroposterior pelvis radiograph and blood metal ion assessment within six months of enrollment. A subset of patients came from a single center that performed MARS MRI at annual follow-up visits regardless of symptoms. This cohort (Sub-Cohort B) consisted of 85 patients. MRIs were assessed for the severity of ALTRs. Multivariable logistic regression analyses were used to investigate the relationship between obesity and elevated blood metal ion levels while controlling for explanatory variables such as; time from surgery, Harris Hip Score, EQ5D, UCLA activity score, acetabular inclination angle, femoral head size, gender, pain, satisfaction, and problems with mobility. Cobalt (Co) ≥ 4.0 ppb and chromium (Cr) levels ≥ 4.6 ppb were considered elevated according to previous literature. BMI values were classified into one of three categories: underweight/normal weight (BMI < 25 kg/m^2), overweight (25 ≤ BMI < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2). Secondly, in the analysis of Sub-Cohort B, outcomes were identified as either moderate or severe ALTR. The same methods used for the analysis of Cohort A were employed.

Results: *ASR HRA* One hundred and thirty-seven patients underwent ASR HRA; 26% were underweight/normal weight, 46% were overweight, and 28% were obese. The median (range) BMI for these patients was 26.8 kg/m^2 (19.5-41.1). Co and Cr values were not statistically different among BMI categories (p = 0.620; p = 0.276) (Figure 1a). There was no difference in the proportion of patients with elevated ions among the three BMI categories (p = 0.540; p = 0.148). Female patients had 3-times increased risk for elevated Co levels (p = 0.019), while patients reporting pain were at 2.3-times increased risk (p = 0.046). Females were 3-times more likely to have elevated Cr levels (p = 0.02). *ASR XL* Two hundred and twenty-three patients were treated with the ASR XL implant; 27% were underweight/normal weight, 34% were overweight, and 40% were obese. The median BMI for these patients was 28.2 kg/m^2 (17.5-54.9). Co and Cr values were not statistically different among the three BMI groups (p = 0.864; p = 0.296) (Figure 1b). There was no difference in the proportion of patients with elevated Co levels among BMI categories (p = 0.257), but underweight/normal weight patients had a higher proportion of patients with elevated Cr levels (p = 0.032). Females were 2.2-times more likely to have elevated Co levels (p = 0.004) and patients reporting dissatisfaction with their THA were 2.1-times more likely to have elevated Co (p = 0.01). Increased time from surgery was associated with elevated Cr levels (OR = 1.3, p = 0.005) and females were at 3.6-times increased risk for elevated Cr (p = 0.001).

Conclusion: Our results demonstrate that patients with high BMI present no increased risk for elevated metal ion levels or development of ALTR. We did find female patients to be at greater risk for elevated blood metal ion levels, which aligns with the findings of other studies. We recommend increased vigilance in the follow-up of female patients implanted with ASR protheses.

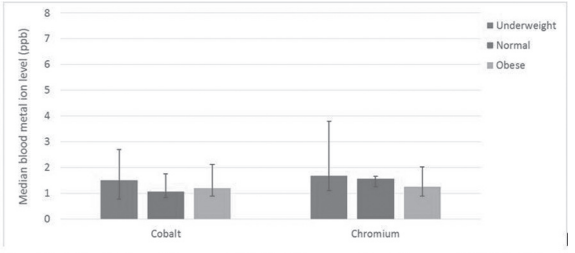

Figure 1a. Median blood metal ion values divided by BMI category for patients treated with ASR HRA. Error bars show 95% confidence interval.

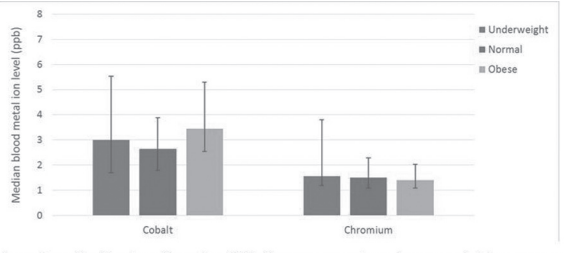

Figure 1b. Median blood metal ion values divided by BMI category for patients treated with ASR XL THA. Error bars show 95% confidence interval.

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Jing Dong, PhD candidate, Dermatology

Implementation of a New GI Screening Paradigm in the Primary Care Setting

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Introduction: Due to the high cost and inconvenience of upper endoscopic biopsy and the rising incidence of esophageal adenocarcinoma, there is currently a need for an improved method for Barrett's esophagus(BE)screening. Ideally, such a test would be applied in the primary care setting and patients referred to endoscopy if the result is suspicious. Tethered capsule endomicroscopy(TCE)is a recently developed technology in the Tearney lab at MGH. It enables rapid acquisition of microscopic images of the entire esophagus in unsedated subjects. Here, we present our experience with clinical translation and feasibility of TCE in a primary care practice(PCP). The acceptance of this device by the PCP staff and subjects shows its potential to be implemented as a new GI screening tool in the PCP setting.

Methods: The TCE device implements optical coherence tomography(OCT)that collects cross-sectional microscopic images of the esophagus at 10(axial)×30(lateral)-μm resolutions. TCE involves swallowing an engineered pill that contains optomechanical components that circumferentially scan the OCT beam inside the body as the pill traverses the luminal organ via peristalsis. The PCP pilot study has two phases:phase 1 focused on testing the safety and feasibility of the TCE procedure. Phase 2, currently ongoing, focuses on improving system portability, capsule fabrication and reusability, and testing a new work flow in the PCP office. TCE device design was derived through an iterative process based on clinical, engineering, and regulatory requirements. In phase 1, a driveshaft based capsule was used together with a large imaging system(Fig 1a, 1c). While from the clinical use perspective, the imaging device was safe, well-tolerated, and allowed high resolution imaging in short procedural time, we received feedback that we should improve the portability and manufacturability of the device. Therefore in phase 2, we have simplified the design and fabrication of the micro-optics and implemented a distal micro motor scanning mechanism(Fig 1d) to increase the manufacturability of the capsule. We have also developed a small and portable OCT system(Fig 1c)with two-fold higher imaging rate. The TCE PCP study is currently approved(IRB P002014-001519) to image adult patients at the Internal Medicine Associates PCP clinic at MGH. Patients scheduled for non-urgent visits to the clinic are eligible to participate. The inclusion criteria includes being over the age of 18 and able to give informed consent. The exclusion criteria includes history of intestinal strictures, symptoms of fever, nausea, dysphagia or sore throat, and pregnancy. The TCE procedure can be performed before or after the scheduled PCP visit. Administration of the TCE device is similar to video capsule endoscopy devices; the non-sedated patient swallows the capsule voluntarily while sipping water. Subjects are given a maximum of five swallowing attempts and offered the option of using Pill Glide™, a flavored lubricant spray. Once swallowed, imaging begins and the capsule operator navigates the device down and up the upper GI tract. When imaging is complete, the capsule is removed through the mouth.

Results: In phase 1, 20 subjects were enrolled 17 were imaged. Total procedural time was 4.8±2.6 minutes. In subjects who successfully swallowed the capsule, 94% said they would definitely recommend the procedure and 6% said they would probably recommend it. Average velocity of ascending imaging was 33.7±16.8 mm/s. Phase 2 is still enrolling patients. In this phase, we've discovered successful capsule swallowing is associated with subject interaction with their PCP;subjects who see their PCP prior to the procedure have a greater swallowing success rate. A final analysis will be conducted when the study finishes. To date, we have enrolled 38 subjects, and successfully imaged 26.TCE examinations show excellent OCT image quality of the esophagus and the upper stomach. We are able to identify features of the normal esophagus such as a layered mucosa(Fig 2a, 2b). In Fig 2b a submucosal dilated gland(green arrow)can be seen emptying to the lumen (blue arrow). One important area to investigate is the transition between the distal esophagus and the proximal stomach, where BE can develop(Fig 2c, 2d). Fig 2c shows the presumably normal appearance of the distal esophagus in a 36-year-old female where layered architecture of the squamous mucosa transitions to gastric cardia(Fig 2e)where a typical "pit pattern" can be seen(blue arrowheads)on the surface of the tissue. This normal transition can be compared to another transition with a somewhat atypical glandular architecture in a 66-year-old female subject. Irregular shaped glands can also be seen in the gastric cardia(Fig 2f)of this subject.

Conclusion: TCE technology has been well received by PCP staff at MGH. Short examination time makes it possible to image patients during their scheduled visit without disturbing the workflow. Feedback received in phase 1 from PCP staff motivated new technological developments that are currently being tested in phase 2 of the study. These include a smaller imaging system and improved TCE device availability. One of the major advantages of TCE procedure is the fact that it does not require extensive preparation. Subjects only need to fast for 4 hours. We also identified the importance of having the subject meet with their PCP prior to attempting the TCE procedure. This finding suggests that improved patient education about the procedure and efforts to decrease anxiety are likely to correspond to higher swallowing rates.

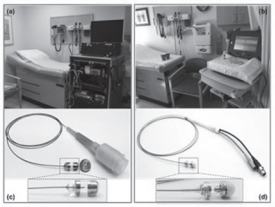

Fig. 1

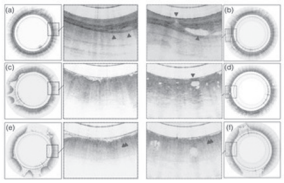

Fig.2

1OCT System & TCE
2TCE Cross-Sectional Frames

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Alysa E. Doyle, PhD, Center for Human Genetic Research (CHGR)

Translating discoveries in ADHD genomics to the clinic

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Introduction: A recent genomewide association study (Demontis et al., submitted) has, for the first time, identified specific susceptibility variants for attention-deficit hyperactivity disorder (ADHD) and confirmed a polygenic component of risk for the condition. We aimed to study ADHD risk variants derived from that study in youth presenting for neuropsychiatric evaluation at an MGH outpatient clinic (the Learning and Emotional Assessment Program; LEAP). Specifically, we sought to determine 1) the convergent validity of ADHD polygenic risk with ADHD-related phenotypes in a diverse clinical sample as well as 2) the association of ADHD polygenic risk with clinical phenotypes that putatively share liability with the condition and that have implications for functional outcome.

Methods: Participants were 923 children and adolescents, ages 7 to 18, consecutively referred for neuropsychiatric evaluation. A subset of these youth (N=470) were genotyped using the Illumina Infinium PsychArray Beadchip. Diagnoses, which were determined subsequent to enrollment, reflected a range of different psychopathological conditions and comorbidity. We determined the polygenic burden of ADHD-related common variants in each patient at different significance thresholds based on the ADHD PGC-iPSYCH meta-analysis. We then associated these risk scores with clinical phenotypes in univariate and multivariate analyses of phenotypes within and beyond the diagnostic category of ADHD. Finally, we conducted a latent profile analysis to examine the association of risk scores with phenotypically distinct subgroups of patients.

Results: The ADHD-PRS predicted the ADHD diagnosis at seven discovery sample thresholds after correction for confounds and multiple testing. The strongest association occurred at discovery sample $p < .000001$ [Wald $X^2(2) = 13.34$, $p=.0013$], where an ADHD PRS score increase of 1.0 SD increased the relative risk of having versus not having ADHD 1.5-fold in youth referred for evaluation. Variation in ADHD risk also predicted cross-diagnostic variation in ADHD symptoms as well as in quantitative measures of aggression and working memory, which are known to confer added risk for poor functional outcome in youth with ADHD. Here, the strongest associations explained 2.3 -3.0% of the variation in these traits. Youth with the highest (i.e. top 30%) ADHD polygenic burden also showed a distinct clinical profile [Wald $X^2(2) = 8.15$, $p=.017$] compared to youth with moderate and low levels of risk. This profile was characterized by greater severity of ADHD symptoms (inattention, hyperactivity, inhibition) as well as symptoms of aggression and anxiety (see Figure 1). Finally, we identified four distinct latent classes of patients characterized by 1) mild symptoms, 2) elevations on internalizing dimensions (depression, anxiety) and psychosis, 3) elevations on ADHD-related symptoms only and 4) high levels of behavioral and emotional dysregulation (including elevated ADHD symptoms as well as aggression, mania and psychosis). In relation to these groups, the ADHD polygenic risk score distinguished the two ADHD-related classes from the mildest class at several discovery sample thresholds after correcting for potential confounders and multiple testing.

Conclusion: In a multi-diagnostic clinical sample, ADHD polygenic risk showed convergent validity with ADHD phenotypes. In genotype and phenotype first analyses, ADHD polygenic burden also associated with traits reflecting cognitive, behavioral and emotional dysregulation that extend beyond ADHD and that have implications for functional outcome. These data underscore the potential relevance of emerging psychiatric genomic discoveries to youth clinical samples and the need for examination of a potential role for genomic medicine in the field of child psychiatry.

Table 1. Multinomial Logistic Regression Using ADHD PRS to Predict Class Membership

ADHD	Class 2 v. 1		Class 3 v. 1		Class 4 v. 1		Main Effect PRS	
Threshold	RRR	*p*	RRR	*p*	RRR	*p*	Wald X^2 (3)	*p*
$p = 5.0 \times 10^{-8}$	1.08	0.64	1.23	0.07	1.21	0.26	3.71	0.30
$p = 1.0 \times 10^{-7}$ †	1.11	0.52	1.42	0.004*	1.47	0.025	10.84	0.0126
$p = 1.0 \times 10^{-6}$ †	1.01	0.96	1.53	0.001*	1.76	0.002*	18.05	0.0004
$p = 1.0 \times 10^{-5}$ †	1.12	0.49	1.44	0.003*	1.68	0.003*	14.16	0.0027
$p = 1.0 \times 10^{-4}$ †	1.06	0.70	1.23	0.09	1.76	0.001*	11.94	0.0076
$p = 0.001$	1.13	0.44	1.24	0.07	1.35	0.07	5.31	0.15
$p = 0.01$	1.19	0.28	1.25	0.05	1.47	0.02	7.38	0.06

RRR = Relative Risk Ratio. Rows with † indicate a significant main effect for PRS after correction for multiple testing; * Asterisks indicate significant RRRs after correction.

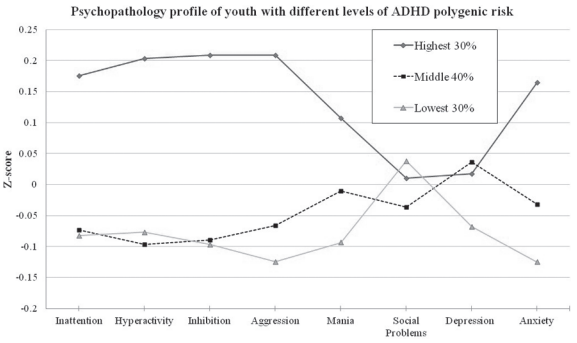

Figure 1.

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Alana Drexler, Surgery - Burn

Prevalence of Parental Concerns during Pediatric Burn Recovery

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Introduction: Burn injuries are among some of the most traumatic events that children can suffer. Parents experience a great of amount of worry and concern about their child's health and recovery following the injury. In this study, we aim to assess the level of parental concern during the child's recovery using the previously established reliable and valid Burn Outcomes Questionnaire (BOQ) following discharge from a hospitalization to up to 18 months later.

Methods: A regional pediatric burn center administered BOQ surveys to children aged 5-18 from 2002 to 2010to assess health outcomes in pediatric burn victims. Children were eligible for the study if they had experienced either at least a 5% total body surface area (TBSA) burn or a burn to a critical area. The BOQ assesses children's physical and psychosocial recovery from burn injuries across twelve domains, including parental concerns (PC). PC is assessed by three questions that assess how often parents are worried or concerned about the following: the child's full recovery from the effects of the burn injury, the child's level of pain and suffering, and the child's future health. Scores on each subscale were normalized with a t- score transformation using data collected from over 1000 patients from the multi-center benchmarking cohort. Means from each subscale were standardized to 50 with a standard deviation of 10. The resulting scores were categorized as either "at risk" or "not at risk". Patients were considered "at risk" on a subscale if they scored lower than one standard deviation below the mean. Surveys were administered at the first return to the clinic after discharge from inpatient care and three, six, and twelve months after discharge. Parents were asked to complete BOQ's at the time of the first outpatient clinic visit following discharge from the inpatient unit after a burn injury and then every 3-6 months thereafter. In this study, we report on data from a subsample of the BOQ validation cases who were from the Boston site of this multicenter study and who had complete data at baseline and the next three BOQ administrations, covering approximately the first 1.5 years after discharge

Results: BOQ surveys were collected from 186 patients at baseline. Among these, 74 patients had four longitudinal BOQ surveys. Of the 186 patients, 32.6% were female and 67.4% were male, 83.4% were English speakers and 16% were native Spanish speakers. The mean age of patients was 8.2±5.32 years old. The mean TBSA was 24±22%. On the PC subscale at baseline, 27% of the patients were "at risk", at the three-month follow-up 17.6% were "at risk", at the six-month 15% were "at risk" and at the twelve-month follow-up 13.3% were "at risk".

Conclusion: The prevalence of "at risk" parental concern decreased at three months after discharge from hospitalization and remained at that level at the six-and twelve -month follow up points. This study provided evidence that in children with burns, parental concern about a child's recovery is relatively common immediately post-discharge (27%) but decreases over the next year or so. However, these findings also highlight the fact that even after about one and one half years, a substantial proportion (13.3%) of parents continue to report high level of concern suggesting a potential need to identify and assess parental concern. Parental concerns are important and salient throughout the entire 18 months of the child's recovery from the burn injury and noteworthy for the clinician to consider.

Table 2. Prevalence of Parental Concern During Recovery.

Time (months)	% at Risk on Parental Concern Subscale (n=74)
0	27.7%
3	17.6%
6	15%
12	13.3%

Table 1. Patient Demographics.

Categorical Variables (n=187)	
Language	
English	83.4%
Spanish	16.0%
Gender	
Male	32.6%
Female	67.4%
TBSA %	
Small (<25%)	41.7%
Medium (25-49.99%)	43.9%
Large (≥60%)	14.4%
Continuous Variables – Means(SD)	
Age	8.2 (5.32) years
Burn Size (%)	22 (24) %

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Steven C. Dufour, Psychiatry

Online yoga as a treatment for mood disorders

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Introduction: Mood disorders, including unipolar depression and bipolar disorder, are impairing, chronic mental health conditions that significantly impact one's everyday life activities. Although effective treatments for mood disorders exist, including pharmacotherapy or psychotherapy, some individuals do not find these options to be sufficiently efficacious or acceptable. There is a need for additional tolerable and easily accessible interventions for treating mood disorders. In-person yoga classes have been shown to promote general physical and mental health as well as improve depression symptoms in unipolar depression and preliminarily in bipolar disorder. Yoga may, thus, be an effective adjunctive treatment for mood disorders. The primary aim of the current study was to examine the feasibility and acceptability of a single online hatha yoga session for individuals with both unipolar and bipolar depression.

Methods: Fifty-six individuals from MoodNetwork, an online community of people with mood disorders, reported being diagnosed with a mood disorder and provided consent for the study, then proceeded to participate in one 30-minute online Hatha yoga class. Forty-four of the 56 (78.6%) individuals completed all components of the yoga class. The average age of participants was 42.0 years (SD = 14.62), and participants were mostly female (93.2%). Participants were asked to rate their affect using the Positive and Negative Affect Scale (PANAS) before and after participating in the online yoga session. Additionally, participants were asked to rate the class on a scale from 1 ("Disliked it very much") to 10 ("Liked it very much") and to complete a qualitative feedback questionnaire.

Results: There was a statistically significant decrease in negative affect from pre- to post-class (t = -6.05; p < .001), but no significant changes in positive affect were found (p > .10). The mean score on the yoga session rating was 7.68 (SD = 1.86), indicating that most participants liked the online class. Most participants (67.9%) reported that they would be "somewhat likely" or "very likely" to participate in an online yoga program again. The majority of comments were positive (57%) on the qualitative feedback questionnaire, emphasizing several benefits, including enjoying the breathing exercises, the clarity of class flow and instruction, and the ease utility of class postures. Furthermore, suggestions for improvement (28% of comments) included adding more instructions/explanations during the class, including more difficult poses for those with greater experience with yoga, and extending the study by creating follow-up videos. Finally, negative responses (15% of comments) included feedback on class structure, discomfort with background audio, and feeling the class pace was too slow.

Conclusion: These preliminary data suggest that online yoga tailored for individuals with mood disorders may be both feasible and acceptable for participants as an adjunctive treatment to outside care. Although immediate effects were not found in boosting positive affect, the brief, 30-minute class provided a relatively large decrease in negative affect that may have significant clinical implications if sustained over multiple sessions. Altogether, given these findings and the ease with which it can be disseminated, online yoga as an intervention for mood disorders warrants further investigation.

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Amy Dushkin, BS, Medicine - Endocrine-Diabetes

Recruitment for Practice-Based Research: The REAL HEALTH-Diabetes Trial

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Introduction: REAL-HEALTH Diabetes adapted an evidence-based complex behavioral lifestyle intervention for weight loss in type 2 diabetes for delivery in primary care. The goal was to conduct the intervention in real-world settings, reaching areas with low SES and high diabetes prevalence. Here, we describe the recruitment effort for the REAL HEALTH-Diabetes Trial from community health centers (CHCs) and other settings. We hypothesized that recruitment yields would be higher at the community health centers, where the intervention was targeted and based, compared to the general primary care population.

Methods: We originally planned to conduct the trial at MGH's community health centers (CHCs) in Chelsea, Charlestown and Revere. In April 2016, recruitment was expanded to all MGH-affiliated primary care practices and endocrinology practices at MGH, Newton Wellesley Hospital and North Shore Medical Center to achieve the recruitment target of 210 in a timely fashion. Patients were identified using diabetes registries. In the CHC setting, we collaborated with CHC co-investigators (CoIs) to approach primary care providers for permission to contact their patients. Non-CHC providers received email requests for permission to contact from the PIs and CoIs. In addition, the study was advertised via waiting room flyers and brochures and Broadcast MGH e-mail. We compared the yields of the recruitment process from the CHCs, general primary care, and endocrinology practices.

Results: A total of 449 health care providers were contacted for 15,203 patients. 84.1% of CHCs and 65.9% of general primary care providers responded for at least one patient (P<0.0001). Endocrinologist response rate exceeded 90%. Screening rate was higher at the CHCs than in general primary care (20.8% vs. 18.4%), but the eligibility rate of those screened was much lower in the CHC population compared to general primary care (12.8 vs. 22.1%, P<0.0001). Of those who were screened and eligible, the enrollment rate of CHC patients was 94.9%, compared to 73.1% of diabetes specialty patients and 67.5% from general primary care (P<0.0001). The overall enrollment rate among patients identified using registries was 1.4%: 1.6% of the CHC population, 1.4% of the general primary care population, and 3.4% of the diabetes specialty population (P=0.28, comparing CHC to general primary care population). Many variables not captured in this analysis contribute to enrollment rates. Reasons for ineligibility will be explored in future analyses.

Conclusion: In this practice-based randomized controlled trial, the collaboration of CHC-based co-investigators and on-site conduct of the intervention was associated with higher CHC-based PCP response rates and higher enrollment rate of eligible CHC patients compared to those from the general primary care population. The population-level enrollment rate was comparable between the health centers and general primary care, despite challenges of enrolling CHC populations in research. Collaborating with practice-based investigators and conducting interventions on site are likely effective strategies to overcome barriers to participation among lower-SES patients.

REAL HEALTH Recruitment

Patients Identified	Overall (N=15,203)	MGH Health Centers (N=4,535)	MGH Diabetes Center (N=553)	MGH Primary Care (N=7,633)	Other Endocrine Practices (N=2,482)	P Value comparing all 4 groups	P Value Health Centers vs. Primary Care
Rate of:							
Any PCP/Endo Response	11,789 (77.5%)	3,815 (84.1%)	509 (92.0%)	5,031 (65.9%)	2,434 (98.1%)	<0001	<0001
PCP/Endo Approved	9,450 (80.2%)	2,911 (76.3%)	380 (74.7%)	3,813 (75.8%)	2,346 (96.4%)	<0001	0.58
Screened of Approved	1,687 (17.1%)	611 (20.8%)	93 (24.2%)	711 (18.4%)	272 (11.6%)	<0001	0.014
Eligible of Screened	290 (17.2%)	78 (12.8%)	26 (28.0%)	157 (22.1%)	29 (10.7%)	<0001	<0001
Enrolled of Eligible	211 (72.8%)	74 (94.9%)	19 (73.1%)	106 (67.5%)	12 (41.4%)	<0001	<0001
Enrolled of identified	1.4%	1.6%	3.4%	1.4%	0.5%	<0001	0.28
Provider Approached	N=449	N=117	N=13	N=312	N=7		
Any response to study contact	310 (67.0%)	102 (87.2%)	13 (100%)	188 (60.3%)	7 (100%)	<0001	<0001
Any patient enrolled	111 (24.7%)	35 (29.9%)	6 (42.2%)	63 (20.2%)	7 (100%)	<0001	0.033

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Odeta Dyrmishi, Masters in Public Administration, Medicine

FeatForward: Preliminary Analysis of participant engagement in a Randomized Controlled Trial of a Multi-modal mHealth Intervention to Improve Physical Activity Behavior in Patients with Cardio-metabolic Risk Factors.

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Introduction: Physical activity is an important modifier of cardio-metabolic risk (CMR) factors and mobile applications are increasingly being used to engage patients to self-manage these risk factors. It is not well known if these interventions are effective for everyone. FeatForward is an ongoing clinical trial to investigate the effects of a mobile application, on physical activity levels and other cardio-metabolic risk factors in patients with chronic conditions. The purpose of this preliminary analysis is to identify the participant characteristics associated with higher levels of engagement with the current study's connected health intervention.

Methods: Intervention FeatForward is a hyper-personalized smartphone app with the ability to respond to individual behavior patterns, simulating an intelligent health coach, to achieve better health outcomes. The app includes machine learning components for tailoring message frequency based on users' activity levels, social networking, and educational features to keep the participants engaged. Additionally, the app has a care provider portal integrated with the medical record enabling physicians to monitor patients' progress and communicate when appropriate. Methods Patients (n=300) with chronic conditions (hypertension, diabetes, obesity) were randomized into two groups: an intervention group that received a Smartphone with the FeatForward app and a Smartwatch to track physical activity and other biometric parameters; and a control group that received a Smartphone with the standard activity tracker app and a Smartwatch. Data collected and analyzed include demographics (age, sex, race & education) and biometric measurements (height, weight, blood pressure, fasting glucose, A1C, cholesterol & CRP protein.) Engagement was measured by participant's continued participation in the study as of study midpoint. In this preliminary analysis we analyzed the differences in the above measurements at baseline (1st visit), between the intervention and control groups for all participants that completed the midpoint visit compared to those that have dropped out/withdrawn/lost to follow up before completing the midpoint. An independent samples t-test was done to calculate differences between groups at the 0 and 3-month time points. Data are presented as mean ± SD or percent.

Results: At the time of analysis, 144 participants were enrolled into the study. Of these, baseline and 3-month data was available for 58 participants. Mean age of enrolled participants at was 56 years (range 19-78). The demographics were similar in both groups with the majority identifying themselves as white (66%), and sex about evenly split. Two-thirds of participants reported having at least high school education and at least 60% reported being employed. Participants who completed the mid-point visit were on average 9 years older compared to those who did not complete the mid-point visit ($p<0.001$). Furthermore, these participants weighed 8 kgs less at enrollment ($p=0.05$), had BMI lower by 3.1 units ($p=0.02$) and waist circumference lower by 6.6 cm ($p=0.01$). There were no other differences in demographic, cardiometabolic or PHQ-8 scores among those who completed the mid-point visit compared to those who did not.

Conclusion: In general, those with continued engagement in the FeatForward study weighed less and had a lower BMI compared to those who ended their participation in the study. This may be indicative of increased motivation to change unhealthy behavior in higher engaged participants. Further research is required to distinguish participant engagement with the intervention itself from that with the trial. FeatForward has completed enrolling participants and we expect to finish complete data collection in 2017.

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Dan-Mikael Ellingsen, PhD, Athinoula A. Martinos Center for Biomedical Imaging

Patient-clinician concordance in social mirroring brain circuitry during pain treatment: A hyperscanning fMRI study

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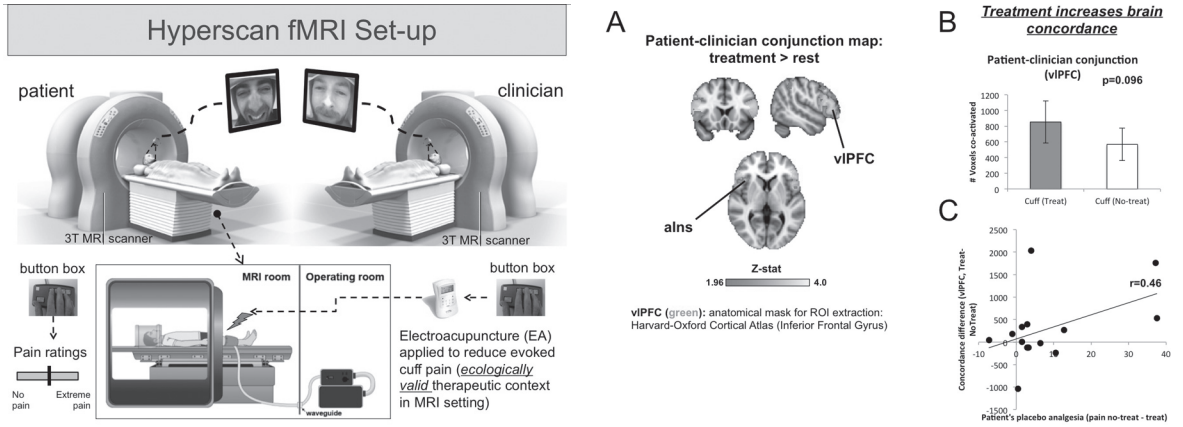
Introduction: The patient-clinician relationship can modulate symptoms such as pain, but the brain basis for this is unknown. Most social neuroscientific studies in humans have employed single-subject methods with artificial "social" stimuli, without an actual social interaction. Correspondingly, most studies on the neural processing, and psychosocial regulation, of pain have focused primarily on the patient. Hence, in order to understand the brain processes underpinning the patient-clinician relationship and how it can modulate pain, we need studies that investigate both parts of the dyad, during an actual social interaction. Here, we simultaneously recorded functional Magnetic Resonance Imaging (fMRI hyperscanning) in patients and clinicians, who interact via video transfer, during clinician-initiated treatment of the patient's pain. We hypothesized concordant activation of circuitry involved in social mirroring, such as ventrolateral Prefrontal Cortex (vlPFC) and anterior Insula (aINS) in both patients and clinicians during pain treatment.

Methods: Patients with chronic pain (fibromyalgia) and clinicians (acupunturists) were enrolled. Each patient was matched with a clinician participant (17 patient-clinician 'dyads'). The patient received a number of moderately painful cuff pressures to the left leg (15 s), while the clinician used a button box to control (real or sham) electroacupuncture stimulation to the patient's leg to treat the cuff pain. Both participants used a Visual Analogue Scale to rate self-pain (patients) or vicarious pain (clinicians) after each trial. Using MRI-compatible cameras, the participants were enabled to communicate non-verbally throughout the scan (See Fig. 1 for overview of study design). fMRI preprocessing included motion correction, skull stripping, correction for magnetic field inhomogeneities, and registration to MNI152. After single-subject GLM analysis, we conducted a group GLM (whole-brain cluster-correction for multiple comparisons) followed by a group conjunction analysis, between patients and clinicians, of the [pain, treatment]>[rest] contrast.

Results: Patients reported decreased pain for both real and sham treatment, compared to overt no-treatment, which was accompanied by reduced ratings of vicarious pain by the clinicians. Patients (receiving pain+treatment) showed activation of posterior (pINS) and mid-anterior (m-aINS) Insula, secondary somatosensory areas (SII), Supplementary Motor Area (SMA), ventrolateral Prefrontal Cortex (vlPFC) dorsolateral prefrontal cortex (dlPFC), and Temporoparietal Junction (TPJ). Clinicians (observing pain+treating) showed activation in aINS, vlPFC, dorsomedial PFC, dlPFC, TPJ, Superior Temporal Sulcus (STS), and primary and secondary visual areas. A conjunction analysis showed activation of vlPFC, aINS, and TPJ for both patients and clinicians during pain and treatment (Fig. 2A), indicating concordant activation of circuitry important for social mirroring in interacting patients and clinicians. A region of interest (ROI) analysis from the area within vlPFC showing significant conjunction, showed a trend toward increased patient-clinician concordance (number of co-activated voxels) during treatment compared to no-treatment (Fig. 2B). Finally, we found that in dyads that showed higher concordance (treatment-no treatment), the patient also showed the strongest analgesia (treatment-no treatment, Fig. 2C).

Conclusion: Using hyperscanning fMRI of patient-clinician dyads, we found a potential two-brain mechanism underpinning social modulation of pain. During clinician-initiated pain treatment of the patient, there was increased patient-clinician concordance in brain circuitry supporting social mirroring, and this concordance was strongest when patients experienced the strongest analgesia. We are planning on completing a total of 40 dyads, and assess how concordance is affected by therapeutic alliance. With a full dataset, we also plan to perform more complex modeling of causal relationships in brain-to-brain communication within dyads.



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Leda Espinoza, BA, Physical Medicine and Rehabilitation

The Influence of Geography on Physical and Psychosocial Functioning After Burn Injury: A Burn Model System National Database Study

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Introduction: Geographic variation in health outcomes in the United States is substantial, however, the specific influence of geography on long-term outcomes after burn injury is an underexplored area. The purpose of this study is to examine regional differences in physical and psychosocial functioning following burn injury.

Methods: Data from the Burn Model System (BMS) National Database collected between 1993 and 2015 were analyzed. Six burn centers in the United States have contributed to this database over the lifespan of the project (1993-present). Three geographic groups within the United States (Northeast, South, and West) were created using a revised breakdown of the American Burn Association regional map. Individuals over the age of 18 that were alive at time of discharge were included. Measures of physical and psychosocial function were assessed at long-term follow-up using the following metrics: Community Integration Questionnaire (CIQ), SF-12 Physical Health Scale (SF-12 PCS), SF-12 Mental Health Scale (SF-12 MCS), Satisfaction with Appearance (SWAP), and Satisfaction with Life (SWL). Mean scores were calculated, and descriptive statistics were generated for demographic and medical data. Omnibus t-tests and chi-square tests were used to evaluate statistical differences in the outcome measures by region. Additionally, multivariate linear regression analyses were utilized to identify differences in outcomes by region, adjusting for age, gender, ethnicity, and burn size.

Results: The study included a total of 3,454 adult burn survivors (Northeast: 696; South: 1277; West: 1481). The population was 74.5% male and had a mean age of 42.4 years and mean burn size of 18.5% total body surface area. There were statistically significant differences by region for the SF-12 PCS, SF-12 MCS, and SWAP at 24 months post-injury (Table 1). In adjusted linear regression analyses, geographic region was a statistically significant predictor of SF-12 PCS, SF-12 MCS, and SWL at 24 months post-injury ($p<0.05$; Table 2). SWAP was approaching significance at 24 months post-injury ($p=0.052$; Table 2).

Conclusion: Geographic region was a statistically significant predictor of social reintegration at 24 months post-burn. Given the limited number of participating centers and the fact that all geographic regions are not represented in the BMS database, additional data is needed to corroborate and verify the generalizability of these findings. Understanding trends in regional influences on burn survivors' long term outcomes can be a useful tool to assess national standards of care and guide resource allocation.

Table 1: Unadjusted Outcome Scores by Region at 24 months post-injury*

Outcome Instrument	Northeast	South	West	p-value
CIQ	7.8 (2.4)	7.6 (2.5)	8.2 (2.5)	0.287
SF-12 PCS	45.9 (10.6)	45.1 (10.7)	47.6 (10.7)	0.007
SF-12 MCS	46.8 (11.4)	46.4 (12.5)	49.3 (11.6)	0.003
SWAP	29.2 (18.7)	31.4 (19.7)	25.6 (17.6)	0.001
SWL	20.5 (7.8)	21.4 (8.9)	22.2 (8.4)	0.091

*All outcome variables are reported as means (SD).

Table 2: Multivariate Linear Regression Analysis Results examining geographic region as a predictor of outcomes at 24 months post-injury

Outcome Instrument	β	p-value
CIQ		
South compared to Northeast	-0.02	0.684
West compared to Northeast	0.33	0.121
SF-12 PCS		
South compared to Northeast	0.04	0.381
West compared to Northeast	0.11	0.009
SF-12 MCS		
South compared to Northeast	0.00	0.983
West compared to Northeast	0.08	0.043
SWAP		
South compared to Northeast	-0.05	0.311
West compared to Northeast	-0.09	0.052
SWL		
South compared to Northeast	0.08	0.093
West compared to Northeast	0.09	0.048

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Brie Falkard, Ph.D., Medicine - Infectious Diseases

Bivalent Oral Cholera Vaccine Induces Memory B Cell Responses

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Introduction: Cholera is an accute dehydrating diarrheal disease caused by infection with *Vibrio cholerae* O1 or O130. It causes signficant morbidity and mortality worldwide. The O1 serogroup is currently the predominant cause of cholera, which is further classified into Ogawa and Inaba serotypes. Cholera is now endemic in Haiti since its introduction in 2010 and is responsible for over 9,000 deaths since the start of the epidemic. A killed whole cell bivalent oral cholera vaccine (BivWC) has been used in multiple countries, following its prequalification by the World Health Organization (WHO) in 2011. The WHO also created a stockpile of the BivWC vaccine to prepare for cholera epidemics in 2013. Despite its current use there are significant gaps in understanding the immune responses stimulated by this vaccine. Previously, our group has demonstrated that Memory B cells (MBC) to *V. cholerae* correlate with protection against cholera in household contacts of cholera patients. Although previous cholera vaccines failed to enduce MBC responses, the current BivWC demonstrates longer clinical protection. The aim of this study is to characterize the MBC responses after BivWC vaccination in a population of Haitian adults.
Methods: Healthy adults, ages 18-60 years old, were invited to participate in the study, located in the Saint Nicolas Hospital, Saint Marc, Haiti. All individuals received two doses of the BivWC vaccine, 14 days apart. Participants were asked to return for blood draws on day 0 (baseline), day 7 (7 days after the first vaccination), day 21 (7 days after the second vaccination), and again on days 44, 90, 180, and 360 following the initial vaccination. Peripheral blood mononuclear (PBMCs) were separated by differential centrifugation and shipped in liquid nitrogen vapor phase to Massachusetts General Hospital, Boston, MA. MBC were quantified from frozen PBMC samples for all time points by an enzyme-linked immunosorbent assay (ELISPOT). MBC responses to *V. cholerae* O-specific polysaccharide (OSP) in the lipopolysaccharide (LPS) were calcuated as a percentage of total MBCs stimulated for IgG and IgA isotypes. Antibody responses to OSP, Ogawa and Inaba, were quantified by ELISA methods from collected plasma.
Results: We observed a significant increase in circulating IgA-MBC responses targeting the OSP, Ogawa and Inaba, of *V. cholerae* O1, starting 21 days following vaccination. We also observed an increase in the level of circulating IgG-MBCs targeting *V. cholerae* O1 Ogawa OSP starting at day 21 and remaining significantly elevated by days 44 and 90. Detected antibodies are also significant elevated over baseline. Inaba and Ogawa specific IgA antibody responses remain significantly elevated until day 44, whereas Ogawa-IgG antibodies stay elevated until day 360.
Conclusion: We found that the BivWC vaccine is capable of stimulating a signficant MBC response, that remains elevated until 3 months after vaccination for IgG-Ogawa serotype. Antibodies detected to IgG-Ogawa OSP were also elevated and continue to stay detectable up to 1 year after vaccination. The Ogawa serotype has been the predominant circulating strain of *Vibrio cholerae* in Haiti since its introduction. The higher level of baseline exposure to the Ogawa serotype is likely contributing to a stronger induction of Ogawa specific responses by the bivalent vaccine. These results provide evidence that the bivalent oral cholera vaccine is capable of inducing and boosting systemic memory B cell responses and long-term antibody responses targeting *V. cholerae*.

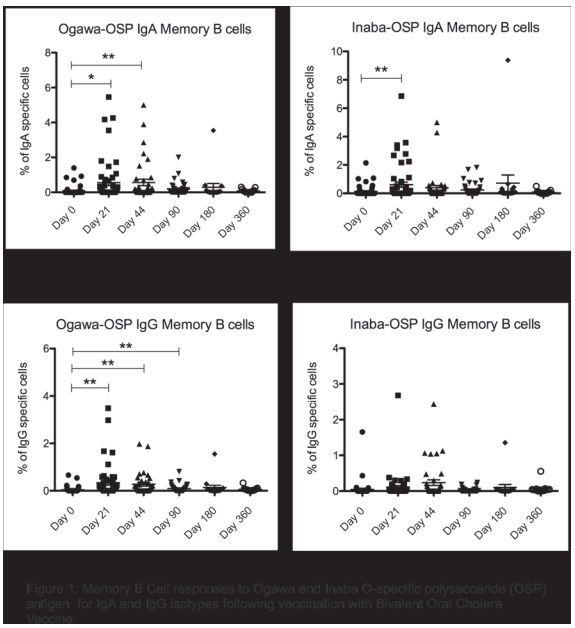

Figure 1: Memory B Cell responses to Ogawa and Inaba O-specific polysaccaride (OSP) antigen for IgA and IgG isotypes following vaccination with Bivalent Oral Cholera Vaccine.

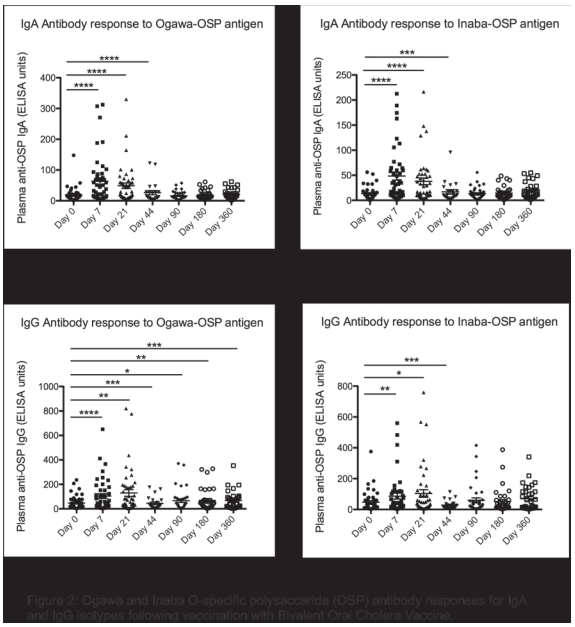

Figure 2: Ogawa and Inaba O-specific polysaccaride (OSP) antibody responses for IgA and IgG isotypes following vaccination with Bivalent Oral Cholera Vaccine.

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Lydia E. Federico, B.A., Psychiatry

Inhibitory control, verbal learning, and cognitive flexibility improve with completion of cognitive-behavioral therapy for PTSD in post-9/11 veterans.

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Introduction: Research suggests that posttraumatic stress disorder (PTSD) is associated with deficits in inhibitory control, verbal learning, and cognitive flexibility (Scheiner et al, 2014; Echiverri-Cohen, A. M., et al., 2016, Keith et al., 2015). Limited data are available to understand whether evidence-based treatments for PTSD can also improve these cognitive deficits. This study seeks to evaluate the impact of evidence-based cognitive behavioral therapy (CBT) for PTSD on inhibitory control, verbal learning, and cognitive flexibility in a post-9/11 veteran population.
Methods: Thirteen post-9/11 veterans presenting to the Home Base program (age *M* = 35.4, *SD* = 7.5, 15.4% female) underwent neurocognitive testing prior to beginning Prolonged Exposure or Cognitive Processing Therapy for PTSD. Neurocognitive measures included the Rey Auditory Verbal Learning Test (RAVLT), a measure of verbal learning and memory, and the Delis-Kaplan Executive Function System Color-Word Interference Test, a two-part measure of inhibitory control (CW-I) and cognitive flexibility and switching (CW-S). Twelve of the thirteen patients were re-assessed within 1 month post-treatment. A subset returned for re-testing 6 months after treatment completion (*N* = 6, including one patient who did not complete post-treatment measures). Neurocognitive outcomes were assessed for improvement using paired Student's t-tests.
Results: Patients showed significant improvement on measures of inhibitory control (CW-I) at post-treatment assessment (10.0(2.4) *vs.* 11.4(2.3), $t(11) = -3.03$, $p = 0.01$), without significant improvement on measures of verbal learning (RAVLT) (73.1(10.1) *vs.* 78.8(8.9)) or cognitive flexibility (CW-S) (9.6(2.9) *vs.* 10.8(2.7)). When compared with pre-treatment scores, the six patients assessed 6 months after treatment completion demonstrated significant improvement on measures of verbal learning (74.3(19.3) *vs.* 88.5(12.1), $t(5) = -2.70$, $p = 0.04$) and inhibitory control (10.7(2.5) *vs.* 12.7(2.1), $t(5) = -3.87$, $p = 0.01$), with a trend towards improvement in cognitive flexibility (10.0(3.4) *vs.* 12.8(1.7), $t(5) = -2.02$, $p = 0.10$). The improvement was significant from post-treatment to 6 month follow up on measures of cognitive flexibility (10.6(2.7) *vs.* 12.6(1.8), $t(4) = -3.2$, $p = 0.03$). However, patients reassessed at 6 months significantly differed from those who were not on verbal learning improvement scores from pre- to post-treatment (15(10.5) *vs.* -0.9(9.9), respectively, $t(10) = -2.68$, $p = 0.02$), suggesting that verbal learning improvement might not only occur from post-treatment to follow up.
Conclusion: These findings suggest that CBT for PTSD is associated with cognitive improvement in the domain of inhibitory control pre- to post-treatment. The subgroup of veterans who completed the 6 month post-treatment assessment demonstrated significant improvement in verbal learning and inhibitory control scores compared to baseline. Most of the improvements in

verbal learning and inhibitory control occurred pre- to post-treatment, with gains sustained at 6 month follow-up. Cognitive flexibility, on the other hand, improved between post-treatment and 6 month follow-up. If replicated in a larger sample, results would support the notion that cognitive performance improves after CBT for PTSD. Because recruitment for the study is still in progress, our main limitations include inadequate power due to missing data and incomplete 6 month follow-up data on two subjects.

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Jennifer A. Felsted, PhD, Dermatology

Longitudinal Healthcare Cost Analyses of Older Patients to Explore Cost Savings Opportunities

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Introduction: Healthcare expenditure in the US is unevenly distributed among individuals in the population. Specifically, half of Medicare reimbursement goes towards caring for the top 5% of the most expensive patients. However, little is known about these patients prior to reaching this top cost segment or how their costs change annually. More insight is needed in order to learn if interventions may target patients before moving to the top 5%. The aim of this retrospective study was to analyze patients' trajectory to the top cost segment and gain insights which may be used to develop hypotheses on how to prevent this upward transition. To do this, we evaluated the following: 1) the total cost of the study population from 2011 to 2015 and its distribution across cost segments, 2) longitudinal trends in cost across cost segments, and 3) the annual variation in number of patients and their cost throughout cost segments.
Methods: Study population was identified through a cross-reference of patients who received care through Partners HealthCare at Home and who were subscribers of the Philips Lifeline personal emergency response service for any duration of time between 2011-2015. Demographic, hospital encounter detail, and cost data were extracted from Partners' Enterprise Data Warehouse. Patients without any 2011-2015 hospital utilization data in the EDW were excluded. We segmented patients into Top-(5%), Middle-(6-50%) and Bottom-(51-100%) segments according to their annual healthcare cost expenditures and organized the segments into cost acuity pyramids. Linear regressions were used to analyze cost trends over time. We developed a Markov chain model of patient transitions from one segment to other segments over 2 successive years. The Markov chain included 3 states (B-bottom, M-middle, T-top segment) and 9 transitions (B-to-B, B-to-M, B-to-T, M-to-B, M-to-M, M-to-T, T-to-B, T-to-M, T-to-T), with states representing the segments of the cost acuity pyramid and transitions indicating the probability that a patient will move from one segment to another over the 2-year period.
Results: We analyzed the cost trends of 2,643 patients, who were predominately elderly (average age = 79), white (93%) females (75%) living independently (94%). Their total cost increased significantly from $17.7M to $33.0M (2011-2015, p=0.003) with the M-segment consistently contributing the highest cost – $2.3M/year (p=0.002). Annual transitions across the cost acuity pyramid showed that 18% of patients moved up (672% cost increase), 22% moved down (86% cost decrease), and 60% stayed at the same segment (18% cost increase).
Conclusion: The M-segment (not the T-segment) contributes the most to overall total healthcare costs from year to year. Patient flow through the segments is fluid, with 40% of patients moving either up or down the cost acuity pyramid annually. Healthcare organizations may see cost savings by identifying and targeting interventions to patients at risk of moving up the cost pyramid, instead of focusing only on those already at the top.

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Jessica Feng, BS, Dermatology

Correlates of Positive Parental Attitudes Towards Indoor Tanning

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Introduction: Skin cancer is the most common malignancy in the United States and exposure to ultraviolet radiation from indoor tanning is an important modifiable risk factor. No national policy currently exists to regulate indoor tanning for minors. Parents who have favorable attitudes toward indoor tanning are more likely to give their adolescent children permission to indoor tan and less likely to support policies to ban indoor tanning for minors. The factors influencing positive parental attitudes towards their adolescent indoor tanning remain poorly understood.

Methods: We conducted a cross-sectional online survey of a national sample of parents of adolescents (ages 11-17) in 2016 (N= 1,205). We assessed parents' attitudes using a 10-item questionnaire on the perceived harms and benefits of indoor tanning for adolescents, and we then averaged items to create a dichotomized, composite measure. The survey also assessed parental tanning behavior, parental and child demographics, and receipt of provider counseling on indoor tanning. We used multivariable logistic regression to assess demographic and behavioral correlates of perceiving low harms or high benefits to indoor tanning.
Results: On multivariable analysis, we found that parents with positive attitudes towards indoor tanning were significantly more likely to be male (odds ratio [OR] 1.8, 95% confidence interval [CI] 1.4-2.3), to have used an indoor tanning devices ≥1 time in the past 12 months (OR 5.9, 95% CI 3.1-11.2), to have no family history of skin cancer (OR 1.4, 95% CI 1.0-1.9), and to have a child with less sun-reactive skin (OR 1.5, 95% CI 1.1-2.0) (all $P<0.05$). Parent age, parent educational attainment, child age, child sex, and healthcare provider counseling on indoor tanning were not associated with positive parental attitudes toward indoor tanning.
Conclusion: This national study identifies populations, such as fathers and indoor tanning users, with more favorable attitudes towards adolescent indoor tanning. Targeted education and outreach may be needed to make these parents more aware of indoor tanning harms and engage them as partners in skin cancer prevention for youth.

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Naomi F. Fields, BA, Medicine

Should we be testing for baseline integrase resistance in patients newly diagnosed with HIV?

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Introduction: Treatment guidelines recommend baseline genotype resistance testing in new HIV diagnoses to guide selection of initial therapy. While integrase strand transfer inhibitors (INSTIs) are recommended for initial treatment, most genotype tests do not assess INSTI resistance (INSTI-R). Given the low rate of transmitted INSTI-R, the value of baseline testing is unclear. We examine the conditions under which INSTI-R testing (IR-testing) might be cost-effective.
Methods: We use a decision tree to compare the 96-week clinical outcomes (QALYs) and cost-effectiveness of two strategies: no IR-testing vs. IR-testing performed at HIV diagnosis. The base case prevalence of transmitted INSTI-resistant (INSTI-R) virus is 0.1%, derived from literature. With no IR-testing, all patients start dolutegravir (DTG)-based ART after genotype. 12- and 96-wk HIV RNA suppression rates for patients on DTG with INSTI-S virus are 90% and 80%, respectively. We presume a 35% probability of success on DTG for those with INSTI-R but without an INSTI-R test, since many INSTI-R isolates are susceptible to DTG. Those not suppressed at 12 weeks undergo IR-testing and change to darunavir (DRV/r)-based ART if diagnosed with INSTI-R virus (96-week suppression, 71%). With IR-testing, all patients are diagnosed with INSTI-S/-R virus prior to ART initiation and start DTG- or DRV/r-based regimens, respectively. Costs include IR-tests ($175) and ART ($41,100-$44,900/year). We examined the impact of key parameters in sensitivity analyses. We labeled a strategy as cost-effective if the incremental cost-effectiveness ratio (Δcosts/ΔQALYs) was ≤$100,000/QALY.
Results: Compared to a no test strategy, IR-testing resulted in worse clinical outcomes (2.34×10^{-6} fewer QALYs) and increased costs by $200/person at 96 weeks. Prevalence of transmitted INSTI-R virus did not affect the favored strategy. When the quality of life for DRV/r treatment was reduced, the preference for no test increased, even when the prevalence of INSTI-R virus was incredibly high (>99%). Even when IR-testing improved clinical outcomes and cost only $5, it was never cost-effective compared to the no IR-testing strategy.
Conclusion: In patients with newly diagnosed HIV, IR-testing is projected to result in worse outcomes and is not cost-effective when compared with a no testing strategy. If INSTI-suppression is possible regardless of INSTI-R, or if avoiding protease inhibitors such as DRV/r will improve the patient's quality of life, the no test strategy is preferred regardless of the prevalence of INSTI-R virus.

Base case results at 96 weeks for INSTI-resistance testing prior to ART initiation among ART-naïve patients.

	QALY	Costs (USD)	ICER (USD/QALY)
No testing	1.754*	$76,200	
Testing	1.754*	$76,400	DOMINATED

INSTI: integrase inhibitor; ART: antiretroviral therapy; QALY: quality-adjusted life-years; ICER: incremental cost-effectiveness ratio. USD: United States Dollars.

*The no testing strategy resulted in 2.34 x 10-6 more QALYs than the testing strategy.

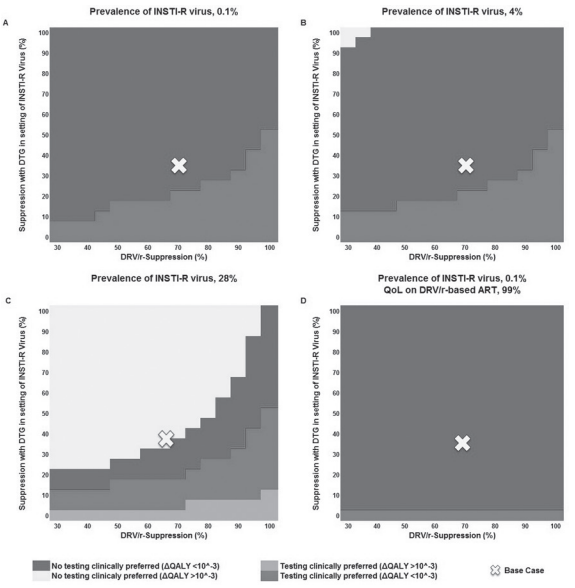

Figure 2

Figure 2. Multivariate sensitivity analysis of the clinical impact (QALYs) of testing for INSTI-R virus prior to ART initiation while varying DRV/r suppression (x-axis), DTG suppression (y-axis), and INSTI-R prevalence levels or QoL on DRV/r-based ART.

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Florian J. Fintelmann, Radiology

Perioperative 3-Dimensional Micro Computed Tomography of Human Surgical Lung Specimens: *A Pilot Study*

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Introduction: Micro computed tomography (micro CT) can generate images at up to 30-times higher resolution than conventional CT and is a non-invasive method to evaluate tissue specimens. Three-dimensional (3D) renderings allow for virtual histology. However, micro CT has not previously been performed on human surgical lung specimens prior to routine pathology workup. Based on the high importance of intraoperative margin assessment during lung cancer resection we hypothesized a role for micro CT in perioperative lung specimen evaluation. Accordingly, the purpose of this pilot study was to assess the feasibility of acquiring micro CT images of human surgical lung specimens in the perioperative setting.
Methods: With approval from the institutional review board, a team of surgeons, radiologists, and pathologists designed a workflow to image human lung specimens after resection and prior to routine pathology workup. Patients who underwent resection of pulmonary nodules or masses suspicious for lung cancer were consented for this study. Specimens were transported directly from the operating room to a micro CT (XT H 225-Nikon; Skyscan 1275-Bruker) located in the pathology laboratory. Images were acquired prior to tissue fixation and routine histological workup. No contrast agent was used. A thoracic radiologist classified target lesions on conventional pre-operative Chest CT and subsequently reviewed micro CT images. Micro CT images were assessed for presence and size of the target lesion, and for distance to surgical margins, both in multiple planes and as a 3D rendering. Findings were correlated to the pathology report. Micro CT images were also assessed for artifacts.
Results: There were 12 males and 9 females (mean age 67 years; range 46-82 years, one patient underwent two different procedures and both specimens were imaged). Procedures included 11 wedge resections, 9 lobectomies and 2 pneumonectomies. Twenty-two lesions (1 cavitary mass, 13 solid and 8 subsolid nodules, including 5 part solid nodules and 3 pure ground glass nodules) were imaged at a resolution of 55 μm (range 23-95). Pathology confirmed 11 adenocarcinomas, 5 squamous cell carcinomas, 1 melanoma metastasis, 1 pancreatic adenocarcinoma metastasis, 2 granulomas, 1 bone malformation and 1 elastotic scar. 3D renderings (**figure 1**) facilitated identification of the target lesion compared to planar images. The target lesion was identified in 12 of 22 cases and comparison to pre-operative CT was made (**figure 2**). Surgical margins could be measured in 11 of these 12 cases. Compared to pathology, micro CT overestimated target lesion size by 3.2% on average (SD +/- 9%) and underestimated surgical margins in malignant cases by 5.1% (SD +/- 9.7%). Differences were not statistically

significant with p = 0.24 for tumor size and p = 0.12 for surgical margins, respectively. Artifacts prevented target lesion identification in 10 cases. Specifically, image quality was degraded by insufficient air-soft tissue contrast (6/10), motion due to specimen deflation (2/10) and detector failure (2/10).
Conclusion: This is the first report of perioperative micro CT of human surgical lung specimens prior to routine pathology workup. Measurement of tumor size and surgical margins on 3D renderings correlate well with histopathology. Specimen preparation needs to be optimized to minimize artifacts. In addition to evaluation of surgical margins and identification of target lesion to speed up intraoperative frozen section of suspected lung cancer, potential future clinical applications include assessment of the degree of invasiveness of lung adenocarcinomas and radiomics.

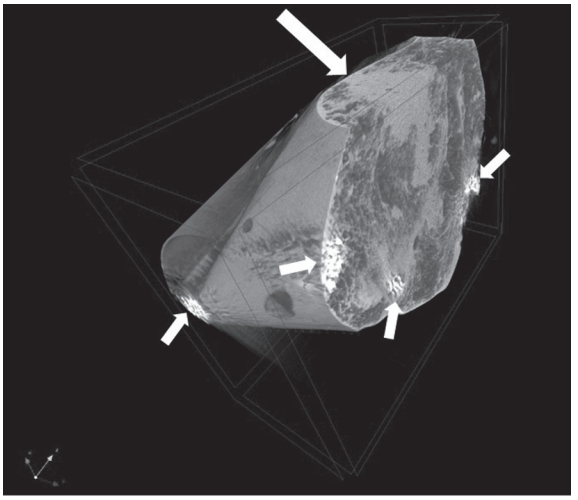

Figure: Three-dimensional rendering of a lung adenocarcinoma (long arrow) in a wedge resection specimen. Note close margin to visceral pleura (<0.1 cm) and peripheral high-attenuation chain sutures (short arrows).

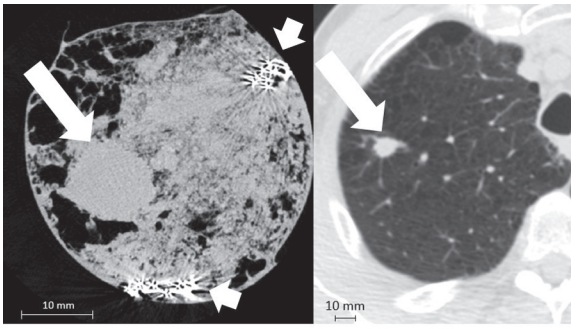

Figure: Micro CT image of benign lung granuloma (left, long arrow) in a wedge resection specimen. Note peripheral high-attenuation chain sutures (short arrows).
Corresponding pre-operative chest CT image (right, granuloma marked by long arrow).

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Zachary J. Finzi, Orthopedics

Changes in Blood Metal Ions after Revision of Failed Metal-on-Metal Hip Arthroplasty

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Introduction: Metal-on-metal (MoM) hip implants have seen a significant decline in their utilization in recent years due to reports of MoM bearing-related complications and high failure rates. While initially marketed as corrosion-resistant and biocompatible implants, MoM bearings wear over time. A biomarker of this wear is elevation of blood cobalt (Co) and chromium (Cr) ion concentrations in the blood. Several previous studies have shown that Co and Cr ion concentrations decline after revision of a MoM bearing surfaces. Patient factors associated with variations in this decline are not yet clear in the literature. The aims of this study were to characterize the changes in blood metal ion concentrations from pre- to post-revision in a cohort of patients treated with a recalled MoM hip system. The secondary aim of this study was to determine if any patient demographic or clinical factors are associated with differences in metal ion level changes from pre- to post-revision.
Methods: A total of 90 patients that underwent revision of either Articular Surface Replacement (ASR) hip resurfacing arthroplasty (HRA)(37) or ASR XL total hip arthroplasty (THA)(53) (DePuy, Warsaw, IN, USA) were included from a prospective, multicenter clinical study. Only patients with one whole blood Co and Cr ion measurement from less than one year prior to revision surgery and one whole blood Co and Cr ion measurement less than 6 months after revision surgery were included. Patients were enrolled at a mean of 6.3 years (range 3.4-10.7) from index surgery with a mean time to revision of 7.5 years (range 4.0-11.5) from index surgery. Multiple reasons for revision were reported, most prevalent of which were presence of adverse local tissue reaction (ALTR) (59%), pain (76%), and osteolysis (59%) in the cohort population. A Wilcoxon Signed Ranks Test was performed on MoM HRA and MoM THA cohorts separately to establish if Co and Cr ion levels changed significantly between pre- and post-revision follow-up. Median Co and Cr levels were plotted at pre-revision, between zero to three months post-revision, and between three to six months post-revision to show changes in ion levels over time. Demographic and clinical variables were age at index surgery, sex, BMI, presence of MoM contralateral implant, revision time from index surgery, reason for revision and blood ion measurement time from revision. Each variable was tested for association with percentage change from pre-revision Co and Cr levels for ASR XL and ASR separately.

Continuous variables and categorical variables were tested using linear regression while dichotomous variables were tested using Mann-Whitney U Tests. A p-value < 0.05 was considered significant.

Results: At post-revision follow-up, Co and Cr decreased significantly from pre-revision levels for both MoM HRA ($p<0.001$ and $p<0.001$, respectively) and MoM THA ($p<0.001$ and $p<0.001$, respectively). Pre- and post-revision ion levels and percentage of pre-revision Co and Cr levels present at post-revision can be found in Table 1. When median post-revision blood Co and Cr levels were split into 0-3 months and 3-6 months and plotted, ion levels drop rapidly between the pre-revision and 0-3 month follow-up, but little change in ion levels were seen between 0-3 month follow-up and 3-6 month follow-up (Figure 1). In univariate analysis, presence of a contralateral MoM implant in MoM THA was significantly associated with higher percentages of metal ion retention at post-revision ($p=0.017$ for Co and $p=0.033$ for Cr). All other tested variables were not associated with Co and Cr retention at post-revision.

Conclusion: Following revision surgery, patients in both ASR and ASR XL cohorts experienced a significant decrease in their Co and Cr ion levels. Although our data does not have the resolution to determine exact ion half-life, our findings suggest that the most rapid decline of ions occurs within 3 months. We also found that Co levels had decreased to a lower percentage of their pre-revision levels than Cr for both implant groups, suggesting that Co is more rapidly cleared from the blood than Cr. Although both cohorts decreased in blood metal ion concentrations, bilateral ASR XL patients retained a higher percentage of pre revision Co and Cr ions. This finding suggests that unilateral revision in bilateral ASR XL patients results in attenuated Co and Cr level decreases due to ions continually generated by the remaining contralateral MoM implant.

Table I: Pre- and post-revision metal ion levels and percentage of pre-revision blood metal ion levels present at post-revision follow-up for ASR and ASR XL cohorts.

Variable	ASR	ASR XL
Pre-revision follow-up time before revision (months)§	3.88 (0.60 - 10.68)	4.32 (0.26 - 10.94)
Post-revision follow-up time after revision (months)§	3.31 (0.62 - 5.88)	3.18 (0.62 - 5.95)
Pre-revision Co (ppb)†	7.73 (0.41 - 199.47)	12.00 (0.77 - 135.77)
Pre-revision Cr (ppb)†	7.06 (0.94 - 74.11)	3.38 (0.63 - 44.32)
Post-revision Co (ppb)†	1.12 (0.18 - 13.67)	1.36 (0.00 - 46.97)
Post-revision Cr (ppb)†	1.79 (0.50 - 15.05)	1.51 (0.00 - 23.80)
Percentage of Pre-revision Co at Post-revision†	21 (03 - 144)	16 (00 - 408)
Percentage of Pre-revision Cr at Post-revision†	29 (04 - 187)	42 (00 - 282)

§ Values given as mean (range). † Values given as median (range).

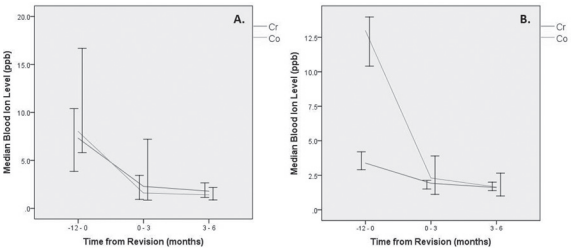

Figure 1: Median blood cobalt (Co) and chromium (Cr) levels in (A) ASR HRA and (B) ASR XL THA patients as a function of time from revision surgery. Each patient is represented once in the pre-revision (-12 - 0) and once in either the 0-3 month or 3-6 month post-revision time point. Error bars represent 95% confidence intervals.

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Nils Fischer, Masters of Public Health, Medicine - Geriatric Medicine

Predictive Modeling of Emergency Care In Elderly Care in Elderly Patients using a Personal Emergency Response System

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Introduction: Predicting which elderly patients at high risk for emergency care could be used to implement targeted interventions to improve patient health outcomes and reduce healthcare costs. Data collected in real-time such as from the Personal Emergency Response System (PERS) could improve current risk prediction models that currently rely on cross-sectional health record data. The objective was to develop and validate predictive models of one-year occurrence of emergency hospital transport, emergency outpatient visit, emergency inpatient admission, and the combined endpoint, based on a combination of PERS and EHR data of elderly patients in a home healthcare program.

Methods: PERS and EHR records of patients in a home healthcare program of a large healthcare organization were matched. Data from 1,868 patients were included in the development and validation of boosted regression tree-based predictive models of risk for emergency care in one year. A total of 991 patients who were PERS users on October 1, 2013 were in the model development cohort, while 877 patients who were PERS users on October 1, 2014 were selected for the validation cohort. Model features were derived from patients' demographic information and two –year clinical histories. Cluster analysis was performed to identify high-risk subgroups with distinctive demographics and clinical utilization patterns.

Results: Performance of the predictive model of emergency hospital transport, as evaluated by area under the receiver operator characteristic (AUC), was 0.71 [0.66-0.75]. AUC was 0.80 [0.76-0.84] for prediction of outpatient emergency visits, 0.82 [0.79-0.86] for emergency inpatient admissions and 0.72[0.68-0.75] for the combined endpoint. Cluster analysis revealed three different high-risk patient profiles with diagnoses of urinary tract infection, chronic obstructive pulmonary disorder, congestive heart failure and atrial fibrillation.

Conclusion: Predictive models of emergency transport could enable timely preventative interventions to high risk patients to improve overall patient experience, higher quality of care, and more efficient resource utilization.

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Exploring the Effects of Technology Enabled Mindfulness and Meditation on Stress Management

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Introduction: Studies suggest that certain technologies may help regulate emotional states and reduce stress. Spire is a wearable device that measures breathing patterns to identify distinct emotional states– calm, tense or focus –to send feedback to the user. Muse is a meditation device that gives real time user audio-feedback based on the EEG wave patterns. The objective of our study was to test the effect of each device on managing stress.
Methods: 126 participants were recruited remotely and randomized to one of two interventions evaluating the Spire (group 1) and Muse (group 2) devices. Each study involved a 2-week baseline period followed by a 6-week intervention. All participants wore the Spire device in the baseline period where it collected data on emotional health (streak data). Then, in group 1, feedback from the Spire device was turned on during the intervention period alerting participants of unfavorable breathing patterns on a companion app. In group 2, feedback from the Spire device remained off for the 6-week intervention period. Additionally, participants in group 2 meditated with the Muse device for 3 to 5 times per week during the intervention period. The Perceived Stress Survey (PSS-14) and Connor-Davidson Stress Resilience Scale (CD-Risc) were administered to all participants at enrollment (Week 1) and closeout (Week 8). Questionnaire and device data from group 1 and 2 were analyzed to determine the effect of each device on mental health outcomes from enrollment to closeout and baseline to intervention, respectively.
Results: In group 1, perceived stress significantly decreased from 23.59 to 20.24 ($p=0.001$) but there was no significant change in stress resilience [(68.25 to 69.5 ($p =0.44$)]. In group 2, perceived stress significantly decreased from 22.49 to 19.15 ($p <0.001$) and stress resilience scores significantly increased from 70.00 to 73.44 ($p=0.014$). Average calm minutes per day using Spire did not significantly change for Group 1 or 2 [61.75 (SD 27.25) to 59.22 (SD 35.24) ($p=0.69$) and 69.72 (SD 29.41) to 63.89 (SD 29.71) ($p=0.13$), respectively]. In Group 1, average focus minutes per day using Spire significantly decreased from 64.15 (SD 31.2) to 50.79 (SD 28.73) ($p=0.001$) minutes but in group 2, the average focus minutes per day as measured Spire did not significantly change [82.38 (SD) to 71.29 (SD 46.55) ($p=0.08$)]. In Group 1, average tense streaks did not significantly decrease [17.63 (SD 16.99) to 14.08 (SD 10.63) ($p =0.15$)]. However, in Group 2, average tense streaks significantly decreased from 18.67 (SD 16.38) to 13.78 (SD 11.71) ($p= 0.004$). After controlling for age, minutes of Spire use, baseline depression, and baseline anxiety in group 1 participants, each day of Spire use was significantly associated with 53.04 ($p=0.02$) more minutes of calm and 62.69 ($p=0.04$) more minutes of focus mind-states. Group 2 participants had 2.9 more tense mind-state minutes ($p=0.02$) with each day of using the Muse device after also controlling for minutes of Muse use, baseline depression, baseline anxiety and age.
Conclusion: Emotion sensing technologies may have a positive role in improving stress management.

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Can Children with Bipolar Disorder Be Identified with an Easy to Use, Inexpensive Assessment Tool?: A Receiver Operating Characteristic Analysis Using the Child Behavior Checklist

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Introduction: Pediatric bipolar (BP) disorder is a prevalent and highly morbid disorder. Efforts at identifying children with this diagnosis in the clinical setting can allow therapeutic approaches to help mitigate the poor outcome associated with this disorder. To this end, the main aim of this study was to assess the diagnostic utility of a unique profile derived from the Child Behavior Checklist (CBCL), an empirically derived, paper and pencil, easy to use assessment instrument, to help identify children with BP disorder in the clinical setting.

Methods: Subjects were derived from four longitudinal studies of youth of both sexes, 6-18 years of age, with and without attention deficit hyperactivity disorder and bipolar disorder (N=674). All subjects had structured clinical interviews with raters who were blinded to subject ascertainment status. A receiver operating characteristic (ROC) analysis was used to examine the ability of the CBCL-BP profile, which consisted of an aggregate T-score of the Attention, Aggression, and Anxiety/Depression scales, to identify those with and without a structured interview derived clinical diagnosis of BP-I disorder in the combined sample.
Results: Of the 674 subjects, 19.3% had a structured interview derived diagnosis of BP-I disorder. A score of ≥195 on the CBCL-BP profile correctly classified 85% of subjects with BP-I disorder with 80% sensitivity and 86% specificity. The area under the curve (AUC) was 0.91.
Conclusion: The robustness of these findings documenting the very strong diagnostic efficiency of the CBCL-BP profile in identifying children with a structured interview derived clinical diagnosis of BP- disorder strongly supports the study hypothesis that children at high risk for a clinical diagnosis of BP-I disorder can be accurately identified with the CBCL-BP profile in the clinical setting.

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Identifying Biomarkers of Response to Proton or Photon Beam Therapy in Pancreatic Cancer Patients

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Introduction: External-beam radiation is often used as a neoadjuvant therapy in the treatment of cancer, with or without radiosensitizing chemotherapy. The goal is to direct ionizing radiation to the tumor in order to induce enough damage to the DNA so that cell death is triggered, while minimizing damage to the surrounding normal tissue. Overall response rates ranging between 60-90% are not uncommon with this approach in solid tumors. Radiation can be delivered to the tumor, in part, in the form of photon beams or proton beams. Protons have the advantage of depositing maximum energy at the end of their path. Since the types of DNA damage elicited by proton beam versus photon beam therapy may differ, underlying biomarkers involving DNA damage pathway mediators may help to selectively direct the use of radiation therapy. We have initiated investigation into these questions using pancreatic tumor samples obtained from patients treated under the clinical trial 11-073 (Phase II Study of Neoadjuvant Accelerated Short Course Radiation Therapy with Proton or Photon Beam, Capecitabine, and Hydroxychloroquine for Resectable Pancreatic Cancer).
Methods: We have developed a focused DNA damage repair (DDR) panel on a Luminex platform to perform RNA expression profiling. A number of biological processes have been represented, including DNA damage (n=95), cell cycle (n=20), ubiquitination/neddylation (n=20), epigenetics (n=6), apoptosis (n=4), and autophagy (n=4). This assay provides the advantage of direct hybridization and signal amplification from a lysate prepared from formalin-fixed, paraffin-embedded (FFPE) tissue, thereby negating bias associated with RNA isolation, cDNA synthesis, and PCR amplification that is required for other RNA profiling approaches. A number of housekeeping genes were evaluated for their ability to normalize the target data. The 11-073 cohort consisted of 50 patients where 38 patients had suitable post-treatment FFPE tissue for RNA expression profiling. For data analysis, the cohort was divided into patients experiencing a pathological response or lack of and those receiving photon versus proton beam therapy.
Results: We identified 5 housekeeping genes that provided optimal data normalization ability across a variety of cancer types. Initial data analysis has identified low expression of mismatch repair mediators (*EME1* and *EXO1*) and overexpression of DNA repair checkpoints (*ATR* and *CHEK1*) as being involved in the determination of pathological response or resistance in a subset of patients, respectively. Although hydroxychloroquine is an inhibitor of autophagy, we identified a complete pathological responder with an autophagy signature that included ATM overexpression. Other signatures from our platform pointed towards potential gene amplification/deletions and altered expression ratios across DDR gene families.
Conclusion: Our custom RNA expression panel has identified discrete alterations in DNA checkpoints and repair mechanisms that are associated with pathological response or resistance to radiation therapy combined with chemotherapy. Ongoing analysis is being pursued to identify a multi-target signature that correlates with pathological response and whether that signature differs between patients treated with photon versus proton beam therapy.

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Simone C. Frank, BA, Medicine - General Internal Medicine

The clinical impact and cost-effectiveness of incorporating point-of-care (POC) assays into early infant HIV diagnosis (EID) programs at 6 weeks of age in Zimbabwe: A model-based analysis

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Introduction: Many EID programs use laboratory-based total nucleic acid (conventional) assays. New POC EID assays are costlier, but may increase access to testing and shorten time to result-return and ART initiation.

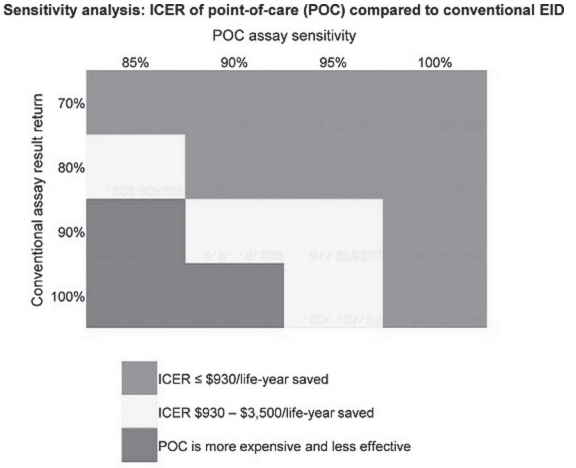
Methods: We used the CEPAC-Pediatric model to examine the clinical benefits, costs, and cost-effectiveness of using POC EID assays at 6 weeks of age in Zimbabwe. We simulated two EID strategies: conventional and POC. Positive results led to ART initiation; ART was stopped if a confirmatory assay of the same type and a third conventional assay (all sent pre-ART) were negative. Modeled assays differed in sensitivity (conventional: 100%; POC: 96.9%), specificity (conventional: 98.8%; POC: 100%), time and probability of result-return (conventional: 1-month delay, 71%; POC: immediate, 97%), and cost (conventional: $15; POC: $21). Model outcomes included early survival, life expectancy (LE), and average lifetime per-person cost for HIV-infected infants and all HIV-exposed infants. We calculated incremental cost-effectiveness ratios (ICERs) using discounted (3%/year) costs and LE for all HIV-exposed infants, defining ICERs ≤$930/life-year saved (Zimbabwe *per-capita* GDP) as cost-effective.

Results: With conventional EID, projected undiscounted LE was 24.95y (HIV-infected infants) and 60.16y (all HIV-exposed infants), at $1,050/HIV-exposed infant (Table). POC EID improved projected undiscounted LE (HIV-infected: 26.58y, HIV-exposed: 60.27y) at $1,120/infant, and increased survival by 4.5% in months 1-2 of life. The ICER of POC vs. conventional was $730/life-year saved (LYS). This ICER remained <$930/LYS if POC specificity was >95% or POC sensitivity was >85%. Large improvements in conventional assay result-return were needed to offset slightly lower POC assay sensitivity (Figure).

Conclusion: POC assays for HIV-exposed infants improve survival and life expectancy and are cost-effective compared to conventional assays. POC assays should be integrated into EID programs in Zimbabwe.

Cost-effectiveness of conventional compared to POC EID testing for infants in Zimbabwe

Strategy for EID testing at 6 weeks of age in Zimbabwe	Outcomes for HIV-infected infants	Outcomes for all HIV-exposed infants (including HIV-infected and HIV-uninfected infants)				
	LE (years, undiscounted)	LE (years, undiscounted)	LE (years, discounted)	Lifetime per-person costs (USD, undiscounted)	Lifetime per-person costs (USD, discounted)	Incremental cost-effectiveness ratio ($/life-year saved)
Conventional	24.95	60.16	24.84	$1,050	$570	Comparator
POC	26.58	60.27	24.91	$1,120	$620	$730



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Deborah Friedman, Psychiatry

Quality of life and mental health outcomes of the CF-CARES primary palliative care model for Cystic Fibrosis

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Introduction: Despite significant therapeutic advances in cystic fibrosis care (CF), CF remains a life-limiting disease with a progressive burden of symptoms and treatments. In this context, individuals with CF are at elevated risk compared to the general population for depression and anxiety, which left untreated, has been associated with poor treatment adherence, reduced health-related quality of life, greater health care utilization and poor health outcomes. Palliative care is an interdisciplinary specialty that seeks to support the best possible quality of life for patients with life-threatening illness. Some have advocated early implementation of palliative care assessment and services for individuals with CF. Historically, however, CF patients have often been introduced to palliative care concepts late in the disease course, with many patients experiencing an abrupt switch from life-prolonging therapies to palliative care services. Innovative approaches to palliative care in CF are needed to provide early symptom management. An early intervention approach is likely to enhance CF self-management and health outcomes, and preserve quality of life. Primary palliative care refers to basic skills that healthcare providers can employ to improve quality of life for patients at any stage of disease. A primary palliative care model in which palliative care is integrated into routine CF care may enable early assessment and intervention. The objective of this study is to pilot an integrated early intervention approach to palliative care in CF.

Methods: Forty-one adolescents and adults with CF participated in a structured assessment including measures of symptom burden, depression, anxiety, health-related quality of life (HRQoL), and a semi-structured interview assessing coping and CF self-management. The assessment guided discussion and referral to supportive services (mental health, alternative health, physical therapy, occupational therapy and enhanced routine care visits) to address burdensome symptoms and improve HRQoL. Follow-up measures were completed at approximately 3 and 6 months post assessment and referral. At the final visit, participants completed a survey assessing satisfaction with the intervention. Intention-to-treat longitudinal regression analyses assessed changes in symptom burden, depression, anxiety and HRQoL. Additional analyses examined outcomes for subgroups participating in mental health (MH) and alternative health (AH) services. Disease severity (severe vs. non-severe disease) was included as a covariate in these analyses.

Results: Acceptability of the intervention was overall favorably rated. Seventy percent of those electing services used them. Analyses including all participants showed a significant decrease over time from initial to post-intervention assessments in depression scores (PHQ-9), with a mean decrease of 1.4 points, and in total number of reported CF-associated symptoms (MSAS-CF). There was a significant increase in HRQoL on the health perceptions subscale (CFQ-R) and a decrease in respiratory symptom-related distress (MSAS-CF) for those with severe disease. Individuals with severe disease who participated in MH services (primarily visits with a psychologist and/or psychiatrist on the CF team) showed a larger 4-point mean drop in PHQ-9. Severe disease was a positive predictor of participation in AH services (acupuncture and/or yoga), and AH participants had significantly higher odds of having no psychological symptom-related distress (MSAS-CF) at follow-up, as well as more sustained positive change in health perceptions.

Conclusion: The CF-CARES (Coping, goal Assessment, and Relief from Evolving CF Symptoms) model, an approach to palliative care that is integrated into routine CF care, appears acceptable to patients, and demonstrated positive preliminary mental health and quality of life outcomes in this pilot. Both severe and non-severe disease subgroups demonstrated positive change. MH services may be particularly beneficial in preventing or treating depression for those with more advanced CF disease.

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Ryan L. Friedman, Bachelors, Surgery - Burn

Challenges to the Standardization of Trauma Data Collection: A Call for Common Data Elements Between Acute and Long-Term Trauma Databases

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Introduction: Trauma encompasses a heterogeneous group of injuries that results in over 3 million hospitalizations and 150,000 deaths per year. Long term trauma outcomes are not well studied but would become a more accessible area of research through the establishment of Common Data Elements (CDEs). CDEs promote data sharing, standardization, and uniform collection which facilitate meta-analysis and comparisons of studies. The purpose of this study was to assess the extent of common data among six representative acute and longitudinal trauma databases from a quantitative and qualitative perspective.

Methods: Data dictionaries of six trauma databases were examined including three acute care databases, the Burn Quality Improvement Program (BQIP), the National Surgical Quality Improvement Program (NSQIP) and the American College of Surgeons - Trauma Quality Improvement Program (ACS -TQIP) and three longitudinal databases the Burn Model System National Database (BMS), the Traumatic Brain Injury Model System National Database (TBIMS), and the Spinal Cord Injury Model System (SCIMS) National Database. Data elements and data values were compared across the six databases. Qualitative and quantitative variations in the data were identified to highlight meaningful differences between datasets. Finally, outcome metrics were analyzed across the three longitudinal databases (BMS, TBIMS and SCIMS).

Results: Twenty-eight data elements were identified with only seven (25%) present in all six databases. The range of existing data elements in each database varied from ten, to twenty-three out of a possible twenty-eight. There are inconsistencies in the data values across the databases. Of the seven common data elements, differences in defined values occur in four of the data elements. The longitudinal databases do not exhibit any common pre-hospitalization measurements. Furthermore, only one of eighteen longterm outcome metrics were present in more than one database.

Conclusion: This study demonstrates inconsistencies in the documentation of data elements in six common data bases for hospitalized trauma patients. The steps needed to achieve data harmonization have been developed by the National Institute of Neurological Disorders and Stroke. A similar collaborative effort is required to develop consensus, and standardize CDEs for trauma research.

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Vincent Galea, Bachelor's, Orthopedics

Evaluation of *in vivo* Wear of Vitamin E Stabilized Highly Cross-linked Polyethylene at Five Years: a Multicenter, RSA Study

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Introduction: Osteolysis secondary to ultra-high molecular weight polyethylene (UHMWPE) wear has been identified as a leading cause of late-term implant failure via aseptic loosening in patients treated with total hip arthroplasty (THA). Efforts to minimize wear and therefore extend the longevity of THA devices *in vivo* have been at the forefront of research. Radiation crosslinking of UHMWPE has been shown to decrease wear. However, the resulting cross-linked polymer (crosslinked-PE) has a high free radical content and is therefore susceptible to oxidation. Several methods have been used to reduce or eliminate the remaining free radicals: melting, heat annealing, or mechanical annealing. An alternative method is chemical stabilization using a free radical scavenger, such as vitamin E. In 2010, vitamin E-doped crosslinked-PE (VEPE) was approved for clinical use in THA. Vitamin E stabilization enhances the long-term oxidative resistance of crosslinked-PE, and *in vitro* studies have shown that this translates to a better retention of mechanical properties and wear performance. The primary purpose of the current study was to evaluate and compare the wear properties of VEPE and one formulation of moderately cross-linked and mechanically annealed UHMWPE using radiostereometric analysis (RSA) in patients five years after their index THA procedure. We also sought to understand the association between polyethylene wear and patient-reported outcome measures (PROMs).

Methods: Three-hundred and five patients from six international centers were recruited into a prospective RSA and clinical outcomes study. Data was uploaded to an academic coordinating research organization (ACRO) via secure online transfer. The patients were treated with implants from a single manufacturer. Seventy-six percent were treated with highly crosslinked

(95 kGy) VEPE liners, and the rest received moderately cross-linked (50 kGy), mechanically annealed liners. PROMs and radiographs were collected postoperatively at one-, two-, three- and 5-year intervals. All plain radiographs were analyzed for component positioning, radiolucency, and osteolysis postoperatively and at each follow-up interval. RSA radiographs were used to analyze the migration of the center of the femoral head relative to the acetabular shell at each follow-up interval. The primary RSA metric considered in this analysis was proximal femoral head penetration.

Results: To date, data from 181 (58%) of the patients have been uploaded to the ACRO (Table 1). At the five-year follow-up, proximal femoral head penetration into the VEPE liners (median = 0.05mm (range, -0.03–1.20)) was significantly lower than the penetration into the moderately cross-linked (ModXL) liners (median = 0.15mm (range, -0.22–1.04)) ($p<0.001$). In the VEPE cohort the median proximal penetration did not increase from the one-year follow-up ($p=0.209$). In contrast, there was a significant increase in femoral head penetration for the ModXL group ($p<0.001$) during that same time (Figure 1). Multivariable linear regression showed that the only variable predictive of increased wear was ModXL liner type ($B=0.12$, $p<0.001$). There were no differences in PROMs between the liner groups, and there was no correlation between polyethylene wear and PROM levels for the cohort as a whole. Six patients have been revised to date; none were revised for aseptic loosening.

Conclusion: The current study is the largest analysis of polyethylene wear at five-year follow-up using the RSA technique. We observed similar bedding in through the one-year interval and wear through the three-year interval between the two liner types, however, there was significantly more wear in the ModXL cohort compared to the VEPE cohort at the five-year follow-up. It will be crucial to continue RSA monitoring in order to understand if these patterns persist at later follow-up. Currently, the wear rates for both liner groups are low and have not lead to any implant failures via aseptic loosening. Continued follow-up will provide a better understanding of the association between wear rate and clinical outcomes.

Table 1. Patient demographic and clinical variables.

	VEPE	ModXL	P Value
Total	231	74	
Total with Data Reported*	123 (53.2)	53 (71.6)	
Female Sex*	42 (34.1)	21 (39.6)	0.412
Age at Surgery (years)†	61 (26-76)	61 (36-74)	0.625
Porous-coated (vs plasma-sprayed) Acetabular Shell	37 (28.9)	26 (49.1)	0.016
32mm (vs 36mm) Femoral Head*	123 (100)	51 (96.2)	0.370
Metal (vs Ceramic) Femoral Head*	99 (77.3)	26 (49.1)	<0.001
PROMs at five-year follow-up			
HHS‡	93 ± 14	96 ± 16	0.094
EQ-5D‡	0.80 ± 0.21	0.85 ± 0.16	0.451
VAS Pain‡	0.5 ± 1.9	0.5 ± 1.5	0.808
VAS Satisfaction‡	0.5 ± 2.8	0.5 ± 2.2	0.723
SF-36 Physical Function‡	50 ± 10	52 ± 8	0.515

* Values given as N (% of liner group). † Values given as mean (range). ‡ Values given as median ± standard deviation.

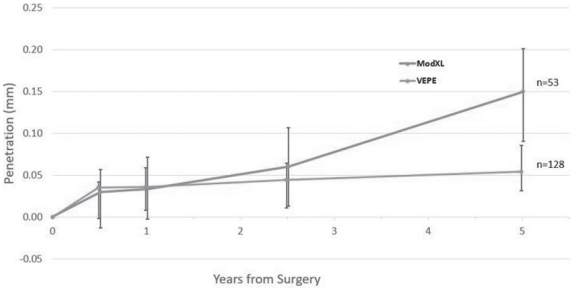

Figure 1. Mean proximal femoral head penetration (mm) into the VEPE and ModXL liners over time with 95% confidence intervals. VEPE, vitamin E-diffused highly cross-linked polyethylene. ModXL, moderately cross-linked and mechanically annealed polyethylene.

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Julia M. Gallagher, MD, Medicine

Integrating Sub-Specialty Home Based Palliative Care Into Primary Care Practices: Preliminary Data on Cost and Hospice Utilization.

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Introduction: The MGH Home Based Palliative Care Program (HBPC) is a Partners Population Health Management (PHM) supported collaborative between Palliative Care and Primary Care. Initial pilot funding was provided to test whether home visits provided by sub-specialty palliative care clinicians closely collaborating with a patient's primary care team would result in: a) improved understanding of patient/family goals of care and alignment of those goals with medical interventions; b) reduced utilization of ED visits and/or hospitalizations and; c) increased hospice utilization and length of stay. Patients living in the community with advanced complex illness, a likely prognosis of less than 12-18 months and enrolled in the Integrated Care Management Program (iCMP) were eligible for referral. Four, geographically contiguous primary care practices with a high concentration of iCMP patients were identified and their physician leaders contacted to assess interest in and feedback regarding the proposed pilot. Follow-up presentations were then made to each practice outlining the pilot including education around criteria for referral such as complex symptom management due to advanced illness and/or complex needs related to advance care planning. A palliative care consultative model was utilized. The program has since expanded to all MGH primary care practices and to a pilot practice within the BWH primary care network. The target patient population has also expanded from the smaller subset of PHM patients enrolled in iCMP to include all PMH_ACO aligned patients. The HBPC program is a multidisciplinary team consisting of a physician medical director, nurse practitioners and a social worker. The

HBPC social worker closely collaborates with the NPs and MD and makes regular home visits to support both patients and their families. All members of the team communicate regularly with the patient's primary care team, iCMP team members, subspecialists and other community based providers in order to design a plan of care for the home that best meets the patient's stated goals and values.

Methods: A total of 240 unique patients were referred to the MGH Home Based Palliative Care (HBPC) Pilot and seen by a HBPC clinician between February 2014 and December 2015. The intervention population was defined as those patients who were seen by a HBPC clinician and had died as of 12/2015. Forty-six patients met these criteria and were included in the original analysis of the pilot. An additional 300 unique patients were seen between January 2016 and June 2017 and an additional 56 patients had died as of 6/2017 for a total of 102 decendents identified for the intervention group. Identification of a control population required propensity-to-treat score matching to produce a subset control population with demographics closer to the intervention group than the full control population. The full control population included those patients who were aligned with the pioneer ACO, enrolled in iCMP, deceased between 2014 and 6/2017, had accessible pre-pilot demographic information including 2013 Impact Pro scores and condition flags and had an MGH PCP who had not referred patients to the HBPC pilot. A propensity-to-treat score was then calculated for each potential control patient and each intervention patient and used to create a 2:1 control to intervention match. Key measures assessed included total medical expenses in the 12 months prior to death, percent of patients referred to hospice prior to death, length of stay on hospice for those patients referred and preliminary cost data.

Results: Total medical expenses (TME) for intervention patients and control patients were calculated for the twelve months prior to death. The average per member per month (PMPM) expenses for months 6-12 was used as the baseline and compared to the average PMPM expenses for month 6 until time of death. Pilot data analysis demonstrated a smaller rate of rise in TME for the intervention population. The observable change was seen at 3 months prior to death with 71% of the difference attributable to inpatient medical costs. Sixty percent of the intervention population transitioned to hospice prior to death compared to 30% of the control population. Intervention patients had a longer average length of stay on hospice and there was a shift away from the 1-5 day hospice length of stay range: 18% of intervention patients had a 1-5 day hospice length of stay compared to 30% of contral patients. Cost analysis demonstrated savings and was done using the estimated 6 month PMPM cost savings, a referral rate of 9 patients per month and the total program cost at the time of one full-time NP and one part-time MD. Preliminary data for the expanded program continues to demonstrate a trend toward lower TME during the final 6 months of life. A full analysis is currently pending.

Conclusion: Our pilot data suggests that a collaborative program between home based sub-specialty trained palliative care clinicians and PCPs in caring for patients with advanced, complex illness and a prognosis of less than 12-18 months is cost effective in an ACO. Preliminary analysis of an expanded program demonstrates a sustained trend toward lower TME in the intervention population. A full analysis including transitions to hospice, length of stay on hospice and program costs is pending. Patient reported outcome measures were not included in our analysis and may have clarified whether a two-fold increase in hospice referrals and a decline in TME near the end of life were associated with an increase in the documentation of patients' goals and values. Future work includes ongoing analysis of cost effectiveness and sustainability, development of PROMS and providers surveys, refinement of patient identification algorithms and collaboration with other PMH community based programs to further foster patient-centered, high value care.

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Abraham Geller, Surgery - Thoracic

Incremental Cost of Complications Following Lobectomy for Stage I Non-Small Cell Lung Cancer

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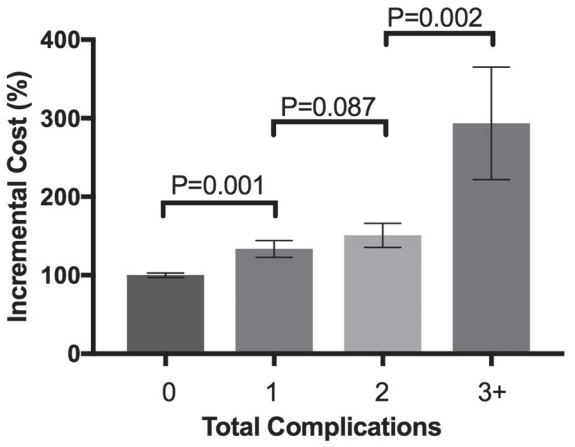
Introduction: Recently, there has been growing interest in the cost impact of complications following surgery, fueled in part by the rapid increase in national healthcare spending and efforts to curb excess costs while improving patient outcomes. While national efforts have long sought to contain healthcare spending, studies have only recently begun to shed light on the cost impact of various surgical procedures and their complications. To date, there is a lack of data quantifying the cost impact of specific complications, both major and minor, over a 90-day postoperative interval. The purpose of this study was to quantify the incidence of several commonly encountered complications following the most common operation for lung cancer (lobectomy), and to estimate the mean incremental cost of relevant specific complications.

Methods: Patients treated with open or VATS lobectomy for stage I NSCLC between 2008 and 2014 were selected. A patient registry was queried for all complications recorded during a 90-day postoperative interval. Complications were sub-classified as major or minor. Hospital billing data for each patient was obtained and queried for all associated direct costs from the procedure until 90 days after surgery, and then concatenated with the clinical data. Patients were excluded if clinical or cost data was unavailable or incomplete for the 90-day postoperative timeframe. All non-stage I cancers were excluded

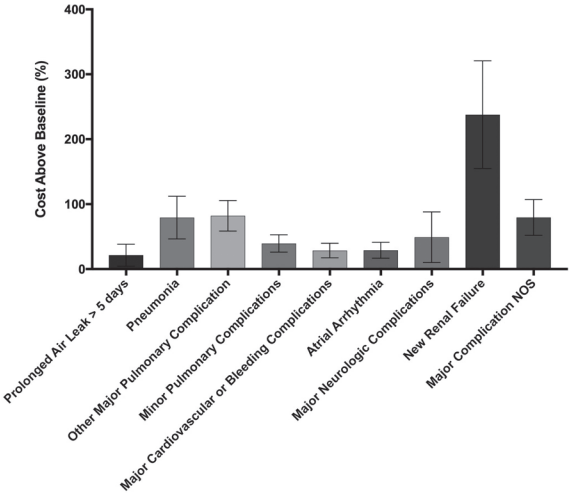
to avoid confounding effects of chemoradiation on adverse outcomes. Univariate linear modeling was used to assess the additive impact of increasing complications on total direct cost. Multiple regression analysis was used to estimate the mean incremental cost of specific complications.

Results: 494 patients were included in this study. 33% experienced ≥1 complication and 17% experienced ≥1 major complication. In patients who experienced complications, atrial arrhythmia (12.8%), prolonged air leak (8.3%), atelectasis requiring bronchoscopy (6.7%), and bleeding/transfusion requirement (6.5%) were most common. Minor complications increased the direct cost of lobectomy by 25.6% (95%CI 18-33%, P<0.001) compared to the cost of an uncomplicated lobectomy. Major complications increased total direct cost by 60.6% (95%CI 54-67%, P<0.001). The greatest predictor of increased 90-day direct cost was renal failure (defined as Cr>2 or Cr>2x baseline), which increased direct cost by 237% (95% CI 186-289%, P<0.001) compared to uncomplicated lobectomy. Prolonged air leak increased cost by 21.4% (95%CI 5-38%, P=0.011) and pneumonia by 79% (95%CI 49-109%, P<0.001).

Conclusion: Complications, both major and minor, contribute significantly to the total 90-day cost of lobectomy for stage I NSCLC. Analysis of 90-day postoperative outcomes more accurately captures costs associated with lobectomy. Renal failure, pneumonia and prolonged air leak harbored the largest incremental cost to an uncomplicated lobectomy. Efforts to control healthcare spending while improving patient outcomes might optimally focus on reducing complications incurring the greatest incremental cost. This work will spawn protocol driven approaches to address the high cost complications.



Additive Impact of Increasing Complications on 90-Day Direct Cost



Incremental Cost of Specific Complications

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Nicholas Z. Georgantas, B.S., Pathology

Frozen Foresight: Rapid *MGMT* and IDH testing in diffuse gliomas initiated at the time of frozen section diagnosis

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Introduction: IDH tumor genotype and *MGMT* promoter methylation status are key factors in the diagnosis and treatment of gliomas, respectively. Knowing IDH tumor genotype is necessary for delivering an integrated diagnosis in the 2016 CNS WHO classification, and also has major prognostic implications. *MGMT* promoter methylation is essential for optimizing treatment decisions in elderly glioblastoma patients, and is increasingly required for clinical trial enrollment. Although the canonical R132H *IDH1* mutation is detectable by immunohistochemistry, *IDH1* and *IDH2* sequencing is required in R132H-immunonegative grade II and III diffuse gliomas and glioblastoma patients <55 years of age. In these cases, time to an integrated final diagnosis can be substantially delayed by the longer turn-around-time required for NGS assays. Similarly, delay in identifying *MGMT* status postpones treatment decisions and possible clinical trial designation.

Methods: To optimize time to final integrated diagnosis and *MGMT* status determination we developed rapid IDH sequencing and *MGMT* promoter PCR protocols that can be initiated at the time of frozen section diagnosis. With optimization of these rapid protocols over multiple departments, IDH sequencing and *MGMT* status results are available approximately 24 hours later, i.e., at the time of review of H&E slides. The majority of these such cases are signed out within 48 hours of the rapid protocol being initiated.

Results: In 49 patients tested since initiation of these rapid protocols, 17 patients (35%) would have met criteria necessitating further IDH molecular testing. Considering standard order practice at our hospital, initiation of these rapid protocols decreased time to integrated diagnosis and *MGMT* status by 82% and reduced cost of IDH testing by 34% as compared to NGS.
Conclusion: Rapid IDH sequencing and *MGMT* PCR initiated at the time of frozen section reduces turn-around-time to final integrated diagnosis and can be more cost effective than NGS for determining IDH status. Initiation of these protocols will thus result in faster results to patients and oncologists as well as more rapid entry into treatment protocols and clinical trials, while reducing overall costs.

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Zohal Ghiaszada, MBA, Massachusetts General Physicians Organization (MGPO)

Implementing Decision Support to Enhance Procedural Appropriateness and Reduce Administrative Burden

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Introduction: Driven by the need to ensure appropriate care for our patients and reduce administrative inefficiencies, Partners Healthcare collaborated with payers to implement Procedure Order Entry (PrOE) for spine procedures. PrOE is a web-based tool that is used to assess the appropriateness of planned surgical procedures. PrOE includes prospective appropriateness assessment, a platform to encourage and document shared decision-making, and personalized consent form displaying patient-specific risks for the procedure. These elements have the potential to reduce avoidable costs while providing a more effective and flexible mechanism than traditional prior authorization to meet patient, physician, and payer goals of providing high-quality appropriate care. Clinical and demographic data documented in selected Epic fields are processed in the PrOE application real-time through algorithms created based on nationally approved guidelines. Through development of these algorithms, a score is generated for completed PrOE assessments and cases are categorized in following three areas: Appropriate, Maybe Appropriate, and or Rarely Appropriate. 2014 data reported from the Agency for Healthcare Research and Quality revealed that nationally, spinal fusion was the costliest procedure performed in the OR setting. Locally, the traditional prior authorization (PA) process for spine surgery was a source of substantial administrative burden for physicians, their teams, and the payer. For an accountable care organization (ACO) like Partners, implementing programs to enhance clinical quality and improve administrative efficiency is a key strategy. Massachusetts General Hospital (MGH) and Brigham and Woman's Hospital (BWH) launched the PrOE program for lumbar spine in September of 2014. As part of this effort, Partners (PHS) Center for Population Health began a "Prior Authorization Waiver" pilot program with BCBS MA, whereby BCBS MA accepts a PrOE assessment as an alternative to the traditional PA for lumbar spine cases to be performed at BWH, MGH, and Newton Wellesley Hospital (NWH) for BCBS MA patients. This program was expanded in December 2016 to include Cervical Spine cases done at BWH, MGH, and NWH for BCBS MA patients. Starting in January 2015 the PA waiver program was adopted by Neighborhood Health Plan (NHP)for lumbar spine cases completed at BWH and MGH. As part of the PrOE PA waiver program, we have established a peer-review process for cases that the system scores as "rarely appropriate." The aim is that as the PrOE program scales across the system, we can offer physicians a tool to assess and document procedural appropriateness in a way that is efficient and engaging.
Methods: (1) PHS provider completes PrOE prior to scheduling surgery. A "PrOE authorization form," auto-populated from PrOE, serves as the paper-based confirmation, which is faxed to the payor, (2) PHS provider submits the completed "PrOE authorization form" to the payor (3) Payor accepts the "PrOE authorization form" and exempts the procedure from its standard PA process (4) BCBS sends PA number to admitting as confirmation.
Results: From October 2014 to March 2017, 580 PrOE assessments have been completed across the PHS network, with a 3% volume increase in 2016 as compared to 2015. PrOE volume has been fairly steady through the transition to Epic. In early stages of the PrOE program, we had 7 spine surgeons using PrOE and throughout the last two years we have onboarded 10 additional spine surgeons. Of the 580 PrOE assessments, 90% of the cases were considered as "Appropriate", 6% as "Maybe Appropriate", and 4% as "Rarely Appropriate". Overall, providers report that they shared decision aids with 84% of the patients. Partners Center for Population Health will continue the collaborations with the stakeholders and payers to assess PrOE adoption and program expansion opportunities. Based on an internal analysis, it has been noted that using PrOE is far easier than the traditional PA process. The PA process with PrOE is estimated to be <24 hours compared to 5 days through the traditional PA process. Completing the PrOE assessment is estimated to take less than 5 minutes compared to 30 minutes with traditional PA, hence saving administrative staff's time.
Conclusion: We believe by expanding PrOE throughout the PHS network, we will retain the role as a national leader in our systematic approach to ensure appropriate care. The PrOE experience demonstrates that collaborative innovations can be implemented to meet the needs of both payer and provider networks.

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Sarah E. Gilpin, PhD, Center for Regenerative Medicine (CRM)

Fibrillin-2 and Tenascin-C Bridge the Age Gap in Human Lung Epithelial Tissue Regeneration

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Introduction: Organ engineering based on native matrix scaffolds involves combining regenerative cell populations with corresponding biological matrices to form functional grafts on-demand. The extracellular matrix (ECM) that is retained following lung decellularization provides essential structure and biophysical cues for whole organ regeneration after recellularization. The unique ECM composition in the early post-natal lung, during active alveologenesis, may possess distinct signals that aid in driving cell adhesion, survival, and proliferation.
Methods: Human lungs from neonatal (aged < 1 week) or adult lung donors (n=3 per group) were decellularized to yield native ECM scaffolds. In-depth fractionated proteomic analysis by mass spectroscopy was used to analyze the ECM composition. The behavior of basal epithelial stem cells (BESCs) isolated from adult human lung tissue was evaluated when cultured on the acellular ECM *in vitro,* and following treatment of lung scaffolds prior to recellularization and *ex vivo* culture.
Results: A significant increase in BESC proliferation and survival was found when cultured on neonatal ECM. Proteomic analysis identified the glycoproteins Fibrillin-2 (FBN-2) and Tenascin-C (TN-C) as potential mediators of the observed effect. BESCs cultured on Collagen Type IV coated plates, supplemented with FBN-2 and TN-C demonstrated significantly increased proliferation and decreased cellular senescence. No significant increase in epithelial-to-mesenchymal transition was observed. *In vitro* migration was also increased by FBN-2 and TN-C treatment. Decellularized lung scaffolds treated with FBN-2 and TN-C prior to re-epithelialization supported greater epithelial proliferation and tissue remodeling. BESC distribution, matrix alignment, and overall tissue morphology was improved on treated lung scaffolds, after 3 and 7 days of *ex vivo* lung culture.
Conclusion: These results demonstrate that scaffold re-epithelialization is enhanced on neonatal lung ECM, and that supplementation of FBN-2 and TN-C to the native scaffold may be a valuable tool in lung tissue regeneration.

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Sara B. Golas, MA, Dermatology

A machine learning model to predict risk of 30-day readmissions in patients with heart failure

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Introduction: In the US, heart failure (HF) is one of the leading causes of hospitalization, particularly in patients aged 65 years and above. Further, approximately 20% of HF patients are readmitted within 30-days following hospital discharge. As major hospital and healthcare systems shift from traditional fee-for-service to value-based care models, there is increasing implementation of strategies to decrease risk of readmission. Accordingly, hospitals that refer patients to HF disease management programs observe lower relative readmission rates. Notable, however, is not all heart failure patients benefit from such intensive programs. Providers are now leveraging advances in big data analytics to develop predictive models that identify specific high-risk patient populations to deliver targeted interventions. An algorithm with high predictive performance may help to identify HF patients who would benefit most from disease management programs. The primary aim of this study was to develop a 30-day readmission risk prediction model for patients admitted with a principal diagnosis of HF.
Methods: We used longitudinal data from electronic medical records of HF patients admitted within the Partners Healthcare system between 2014-2015. Feature vectors used as model inputs included structured demographic, encounter, diagnosis, procedure, medication, and laboratory data, and selected extracts of un-structured data from ambulatory notes and discharge summaries. Test data pre-processing included sentence splitting, lemmatization, part of speech filtering, frequency filtering, and generating term frequency. Deep unified networks (DUNs) – a new mesh-like network structure of deep learning with vertical and horizontal connections of neurons to avoid over-fitting – was prepared to develop the risk prediction model. 10-fold cross-validation was used to validate the model. Overall model performance was assessed using the concordance statistic. We also selected a discrimination threshold based on maximum projected cost saving to our healthcare system.
Results: Data from 11,510 patients with 27,306 admissions and 6,369 30-day readmissions was used to train the model. Patients were primarily older (average age 69 yrs), white (84.5%), married/partnered (45.6%), retired (57.3%), and not

college-educated (51.4%). Data processing reduced the number of variables to be used in the algorithm by 82%, the final algorithm included 3,512 variables. Concordance statistic for the model is area under curve (AUC) 0.706, with an accuracy of 76.7% at the classification threshold that corresponds with maximum cost saving.
Conclusion: Deep learning can be applied to structured and unstructured EHR data to predict 30-day readmissions in patients with CHF which could enable the precise delivery of targeted interventions to the highest risk patients.

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Sarah K. Golden, BS candidate, Surgery - Burn

Collecting Patient Reported Outcomes in Honduran Children with Burns

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Introduction: During a recent outreach visit to Honduras, a bilingual Clinical Research Coordinator accompanied clinicians from Shriners Hospitals for Children—Boston in order to collect Burn Outcome Questionnaires from Spanish-speaking parents of patients being treated at the outreach clinic. The Burn Outcome Questionnaires are widely-used, burn-specific health outcomes questionnaires that assess patients' physical and psychosocial recovery from burn injuries across twelve separate domains. The twelve domains assess levels of pain, itch, capability to participate in physical sports, ability to use upper extremities, ease of transfers and mobility, compliance with medical treatment, perception of post-burn appearance, family dynamics, parental concerns, child emotions, school reentry, and satisfaction with treatment. BOQs are available in both English and Spanish and have been used for over 15 years to monitor patient progress and create individual recovery curves. The BOQs analyzed were designed specifically to assess the recovery of patients aged 5-18. The questionnaires were completed by parents, and the data is known as parent-reported outcome measures (PROMs). Analysis of aggregate PROMs data collected in Honduras can reveal the domains in which patients experience collective success or struggling. The aim of this data collection and analysis was to better assess the needs of patients at the clinic in Honduras. Since international outreach visits are routinely conducted, administering PROMs can lead to more effective patient treatment over time.
Methods: Aggregate data from the 29 5-18 BOQs administered was analyzed by the subscores of each of the twelve domains of questions. Based on responses to the BOQ questions, average subscores among respondents for each domain were calculated by TonicHealth© software. The aggregate data indicated the number of respondents with below average, average, and above average scores for each category based on their answers to each item. Below average subscores were defined by -10 to 39.9 points and indicated struggle of the child or family in a particular aspect of recovery. Average scores, ranging from 40 to 59.99 points, demonstrated adequacy; above average scores (60-80 points) showed excellence in a subscore. Additional data provided from TonicHealth© software included the most frequent score among the 29 respondents for each domain's subscore as well as the maximum, minimum, and average score. This data was analyzed to assess the areas of recovery in which the Honduran patients struggled the most and in which areas they were experiencing the greatest success. Graphs were created to analyze the percentages of scores in each category that were below the average range. This data was then compared across domains. Furthermore, the mean scores for each domain were compared. The two lowest subscores among respondents were identified using both the average score and the percent of respondents with a score below the mean range. Moreover, by comparing the subscore averages, the three domains with the highest mean subscores were identified.
Results: A comparison of the average scores for each domain revealed little variation among the majority of the different mean subscores. However, the compliance, satisfaction, and school mean scores were notably higher than the rest. The overall average score among all domains was 56. The average scores for compliance, satisfaction, and school were 63, 66, and 67, respectively, while none of the other domains had an average above 54. Additionally, a comparison of the percentage of scores in each domain below the overall average range demonstrated that itch and pain were the domains in which the greatest number of parents reported struggling of their child. Across all domains, the mean percentage of scores below the average range was 8%. The percentage for pain and itch were 17% and 24%, respectively, while none of the other domains had a percentage of below average scores above 11%.
Conclusion: The analysis of the PROMs data reveals the presence of certain subscores that indicate either collective patient success or struggling in a particular domain. Averages of the respondents' scores demonstrate that the areas in which the greatest number of patients report good outcomes are compliance with medical treatment, school reintegration, and satisfaction with treatment. Conversely, the itch and pain domains presented the largest percentages of scores below the overall mean range, indicating that patients generally struggled more with these aspects of post-burn life. These results may prove useful for clinicians in improving the care of Honduran patients on future outreach visits. Since many patients reported issues with pain and itch, treatment could be adjusted to better mitigate these symptoms. Anecdotally, itch is very problematic in Honduras as a result of the hot climate. Perhaps additional interventions to attenuate itch should be implemented in the

treatment of Honduran patients. This initial analysis reveals the ability of PROMs data to highlight the areas of care that need the most improvement and those that already lead to excellent outcomes. Additional research could focus on comparing the PROMs data collected in Honduras to the data collected in the United States in order to better tailor treatment to Honduran patients on future outreach trips.

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Alexander Goudriaan, MD, Orthopedics

Neutrophil/lymphocyte and platelet/lymphocyte ratios as prognostic predictors for survival in patients having osseous metastases secondary to lung cancer.

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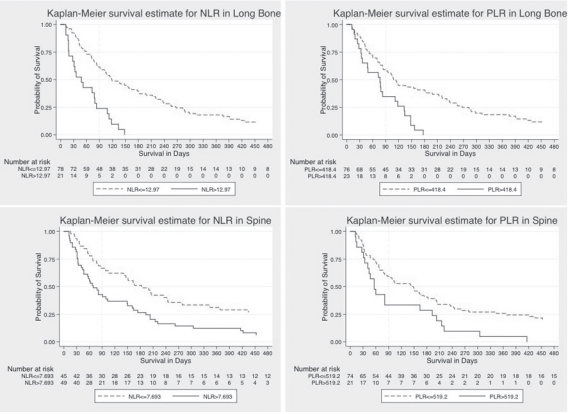
Introduction: The prevalence of cancer continues to increase in the United States. Metastatic disease to bone is a significant cause of disability and it is estimated that over 80% of patients having cancer will develop spinal metastases. Most spinal metastases do not warrant treatment. However, pathologic fracture with or without spinal cord compression can be symptomatic. Treatment of patients with spinal or long bone metastases must be predicated by an understanding of their survival probability. However, predicting survival can be quite difficult, particularly in patients with lung cancer. Determining which patient will benefit from invasive procedure versus those who would be better suited in hospice due to the morbidity of said procedure is important. Numerous studies report the association between poor survival outcomes in cancer and neutrophil:lymphocyte ratio (NLR) or platelet:lymphocyte ratio (PLR). This can be explained by micro environmental changes due to inflammation and systematic immune effects. As NLR and PLR seem to be predictors of survival, we aim to analyze ideal cut-off values for predicting survival of patients having osseous metastasized lung cancer.

Methods: In this retrospective study (2002-2015) from two tertiary care referral centers we included 130 patients with long bone and 127 patients with spine metastases secondary to non-small cell lung cancer. Survival time was calculated as the interval between operative treatment for (impending) fracture and death or final follow-up. For both groups the optimal cut-off values for pre-operative NLR and PLR were dichotomized according to receiver operating curve analyses. Survival curves were plotted according to the Kaplan-Meier method. The association between NLR or PLR and survival was assessed using Cox proportional hazard regression analyses. A p-value of <0.05 was considered statistically significant.

Results: Median and mean survival for both groups was 118 and 299 days, with a range of 8 to 4940 days. In both groups, long bone and spine, an elevated NLR and PLR predicted a significantly worse outcome of overall survival. Compared with the elevated groups, median survival time was >2.45 times longer for the non-elevated NLR subject groups. The ideal cut-off value for NLR in long bone is 12.97 (HR 3.428, 95%CI: 2.011-5.843; P=0.000) and for PLR 418.4 (HR 2.406, 95%CI: 1.446-4.004; P=0.001). For spine it is 7.693 (HR 2.151, 95%CI: 1.388-3.334; P=0.001) and 519.2 (HR 1.957, 95% CI: 1.179-3.249; P=0.009), respectively. The difference in estimated probability of survival at 90 days after operation was >0.23 for both NLR and PLR in long bone and spine groups.

Conclusion: The decision of operative treatment in case of osseous metastasized cancer is often based on the chance of surviving the 2-3 month period after operation. As this decision is intended to improve quality of residual life, it is important to have precise prediction models. In this study NLR and PLR cut-off values for osseous metastasized lung cancer showed significant differences in survival, especially in the 'critical period' of 2-3 months after operation striking differences were found. NLR and PLR should therefore be regarded as important prognostic factors, which must be included in prognostic survival algorithms for lung cancer.



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Jeremy Goverman, MD, Surgery - Burn

Presence of Neutrophil Extracellular Traps (NETs) in Human Burn Wounds

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Introduction: Neutrophils are the first line of defense and are rapidly recruited to sites of injury. Activated neutrophils can release neutrophil extracellular traps (NETs) that are composed of decondensed chromatin and cytotoxic granular proteins. Recently, NETs were found to be present in mouse full thickness excisional skin wounds and they inhibit wound healing. Deficiency in NET formation or cleaving the DNA backbone of NETs with DNase 1 accelerates wound repair in mice. Burn injuries constitute the second most common cause of trauma-related deaths in both developing and developed world. It remains unexplored whether NETs are also present in human burn wounds, which may have impact on burn-induced inflammation, burn wound healing, and skin graft outcomes. The purpose of this study was to examine human burn wounds for the presence of NETs.

Methods: Excess human burn wound tissue, which was typically discarded, was cryopreserved for immunofluorescence staining for NET biomarkers (citrullinated histone H3, H3Cit), myeloperoxidase (MPO) and peptidylarginine deiminase 4 (PAD4, a key enzyme that citrullinates histone H3 and thereby decondenses chromatin), or embedded in paraffin and sectioned for H&E staining. We evaluated five types of specimens: control (intact skin away from burn area), wound base, eschar, allografts after placement and hypertrophic scar.

Results: Immunofluorescence staining revealed the presence of extracellular H3Cit and DNA in MPO and PAD4-positive areas of a wound base specimen (12 days post flame injury) and a heavily colonized allograft (11 days post contact injury). Presence of extracellular DNA was also observed with H&E staining. NETs were absent in control skin, eschar and hypertrophic scar.

Conclusion: NETs can form in wound base and allografts after placement. We are now characterizing the time course of NET formation in burn wounds and whether it can serve as an early indicator of delayed burn wound healing and/or skin graft loss.

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Lipika Goyal, Medicine - MGH Cancer Center

Polyclonal secondary FGFR2 mutations drive acquired resistance to FGFR inhibition in patients with FGFR2 fusion-positive cholangiocarcinoma

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Introduction: Genetic alterations in the fibroblast growth factor receptor (FGFR) pathway are emerging as promising therapeutic targets in a broad range of cancers, including intrahepatic cholangiocarcinoma (ICC). No targeted therapies are currently approved in ICC, but the recent discovery of FGFR2 fusions in 10-20% of ICC tumors has prompted the evaluation of FGFR inhibitors in this disease. The selective FGFR inhibitor BGJ-398 displayed encouraging efficacy in a phase II trial of previously treated patients with ICC harboring *FGFR* aberrations with a preliminary response rate of 22%. However, as seen with other targeted therapies, acquired resistance inevitably developed. To identify potential mechanisms of resistance, we analyzed serial blood and tissue samples of patients with ICC treated on this phase II trial at the Massachusetts General Hospital Cancer Center.

Methods: We collected pre-treatment and post-progression plasma and tissue samples from three patients with FGFR2 fusion positive ICC treated with BGJ398 for up to 8 months who all had tumor shrinkage of 28 to 49% by RECIST version 1.1 criteria followed by disease progression. In plasma, cell-free circulating tumor DNA (cfDNA) was analyzed for mutations in 70 cancer-related genes using the digital sequencing-based Guardant360 assay. Tumor tissue was assessed with targeted deep-sequencing of 315 cancer-related genes with >500 fold coverage using the FoundationOne assay. Rapid autopsy was conducted on one patient, and twelve distinct lung and liver metastasis were harvested for analysis. Fusion events were

detected with the MGH Solid Fusion Assay (SFA), a CLIA-certified assay detecting fusion events in over 50 cancer-related genes. The sensitivity of individual resistant clones was compared to a panel of five FGFR inhibitors in clinical trials, as well as the irreversible inhibitor FIIN-2.

Results: Serial analysis of cfDNA revealed multiple recurrent point mutations in the *FGFR2* kinase domain at progression (Figure 1). The gatekeeper mutation, p. V564F, sterically hinders drug binding and was identified in all 3 patients. The other *FGFR2* mutations identified were also functionally relevant residues including p. N549H/K, p. E565A and p. K641R which disengage the molecular brake that otherwise maintains the kinase in an inactive conformation, and p. K659M and p. L617V, which lead to stabilization of the active conformation. A rapid autopsy was performed in patient #2 to genomically characterize multiple metastatic sites given that five different FGFR2 mutations were detected in the post-progression cfDNA but only one was identified in the post-progression biopsy. Targeted deep sequencing of 12 metastatic lesions revealed marked inter- and intra-lesional heterogeneity, with different *FGFR2* mutations in individual resistant clones Figure 2. Molecular modeling and *in vitro* studies indicated that each mutation identified led to BGJ398 resistance and was surmountable by structurally distinct FGFR inhibitors. In the panel of 6 FGFR inhibitors tested, LY2874455 and dovitinib appeared to be least affected by the p.V555M gatekeeper mutation (Table 1).

Conclusion: To our knowledge, this study is the first to define mechanisms underlying clinical acquired resistance to FGFR inhibitor therapy. These data suggest that secondary *FGFR2* kinase domain mutations are an important mechanism of clinical acquired resistance, and that alternative FGFR inhibitors capable of overcoming these mutations may be important future clinical strategies for these cancers.

Figure 1

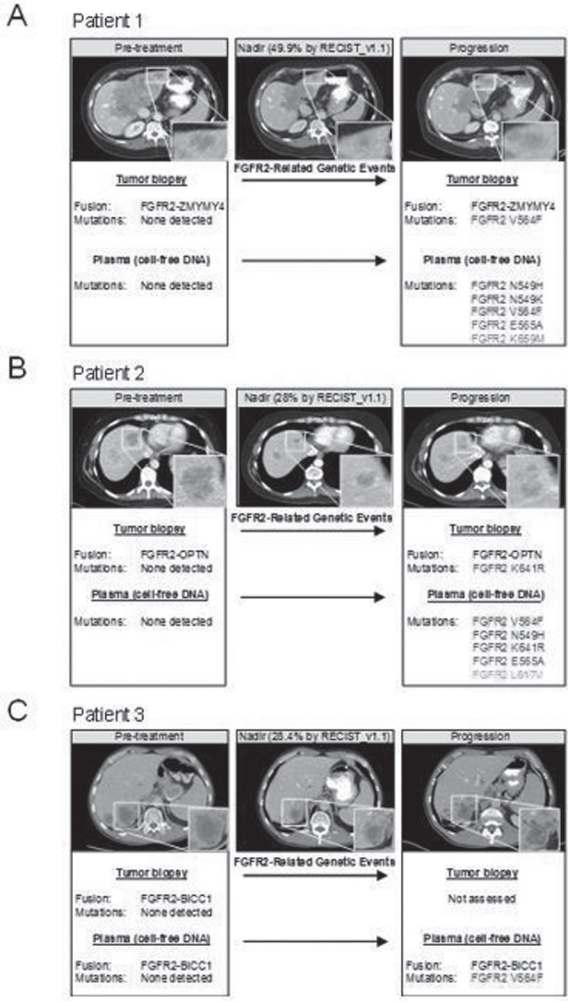

Figure 1. Clinical Acquired Resistance to BGJ398. CT scans demonstrating initial response lesions that subsequently progressed despite BGJ398 therapy for Patient #1 (A), Patient #2 (B), and Patient #3 (C). *FGFR2*-related genetic events detected by Solid Fusion Assay (SFA), whole exome sequencing, and the cfDNA analysis are documented in the text below CT images.

Figure 2

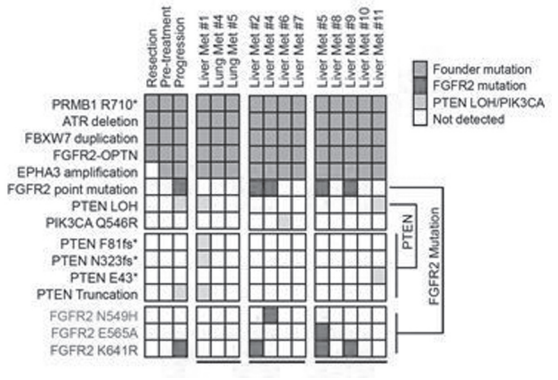

Figure 2. Rapid autopsy reveals inter-tumoral and intra-tumoral heterogeneity of resistance. A. Heatmap illustrating mutations detected in the indicated autopsy lesions. Three distinct *FGFR2* kinase domain mutations and four distinct PTEN mutations were identified.

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Jonathan Greenberg, PhD, Psychiatry

Reduced interference in working memory following mindfulness training associated with increases in hippocampal volume

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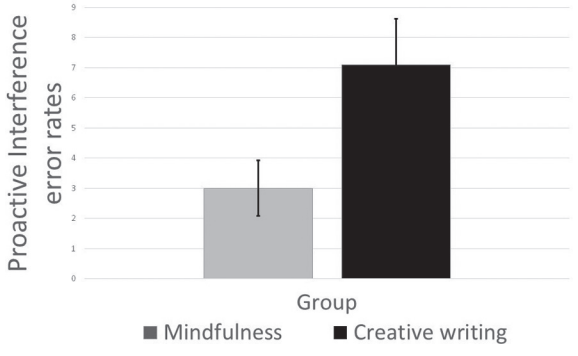
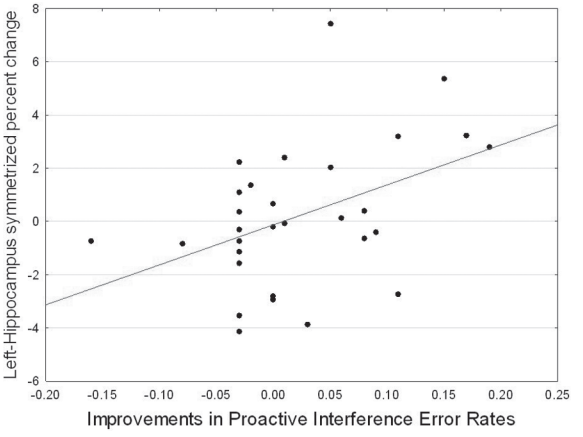
Introduction: Proactive interference occurs when past memories interfere with retaining newer material. It is one of the main reasons of forgetting from working memory, and successful resolution of proactive interference is critical for reasoning, learning and problem solving, and has been linked to the hippocampus. However, little is known about how this ability can be improved. Mindfulness training emphasizes focusing on the present moment and minimizing distraction from competing thoughts and memories. It has been found to improve working memory and increase hippocampal density. The current study examined whether mindfulness training can reduce proactive interference in working memory and whether such improvements are associated with changes in hippocampal volume.

Methods: 87 participants were randomized to a four-week web-based mindfulness training program or a similarly structured creative writing active control program. Before and after the programs participants' brains were scanned via a Siemans 3T scanner, and the Recent Probes computer task measuring proactive interference was administered.

Results: The mindfulness group exhibited significantly greater accuracy in proactive interference resolution compared to the active control group following training, and these improvements were significantly associated with volume increases in the left hippocampus

Conclusion: Results provide the first evidence suggesting that mindfulness training can protect against proactive interference, and that these benefits are related to volumetric increases in the left hippocampus. In light of these results, it is suggested that mindfulness may be particularly beneficial for individuals with conditions typically characterized by impairments to working memory and reduced hippocampal volume such as aging, depression, PTSD and childhood maltreatment or trauma.





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Kelsy E. Greenwald, MD, Emergency

Feasibility and acceptability of home-based HIV testing among refugees: A pilot study in Nakivale Refugee Settlement in southwestern Uganda

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Introduction: Refugees in sub-Saharan Africa risk exposure to HIV and many struggle to access HIV testing. Home-based HIV testing may help refugees overcome obstacles to testing. In 2013, our research team completed a routine clinic-based HIV testing study in Nakivale Refugee Settlement in southwestern Uganda, demonstrating increased numbers of HIV-positive individuals identified per week with routine testing. For this pilot, we conducted home-based HIV testing to determine the acceptability and feasibility of this testing strategy and to compare demographics of home-based and clinic-based HIV testers in a refugee settlement.

Methods: From February-March 2014, we visited homes up to 3 times on different days of the week and different times of day in 3 geographic zones within Nakivale. We enrolled adults greater than or equal to 18 years of age who spoke English, Kinyarwanda, Runyankore, or Kiswahili and surveyed them about their socio-demographic characteristics. We used the proportion of eligible participants encountered at home to demonstrate feasibility and the proportion willing to participate in HIV testing to demonstrate acceptability. We used logistic regression models with the generalized estimating equations approach to correlate willingness to test with gender and with the number of eligible individuals present in the household at time of consent, while taking into account clustering within households. Characteristics of home-based and clinic-based testers were compared using Wilcoxon rank sum tests and Pearson's chi-square tests.

Results: Of 319 homes visited with 566 eligible individuals reported living in these homes, 292 homes (92%) had 507 (90%) individuals present; 353 (62%) present at visit one, 127 (22%) additional people at visit two, and 27 (5%) additional people at visit three. Home-based HIV testing participants totaled 378 (75%); all received their results and 7 (1.9%) had new HIV diagnoses. For each additional person present at home, the odds of participating in HIV testing increased (OR 1.52, p=0.007). There was no difference in willingness to test by gender (p=0.66). Of participants, 134 (35%) were from the Democratic Republic of the Congo, 129 (34%) from Rwanda, 91 (24%) from Burundi, and 23 (6%) from Uganda. Participants were predominantly female (56%), with a median age of 30 (IQR 24-40) and a median time of 6 years (IQR 3-8) in Nakivale. Compared to clinic-based testers, home-based testers were older (median age 30 [IQR 24-40] vs 28 [IQR 22-37], p<0.001), more likely refugee (93% vs 79%, <0.001), and more likely to live ≥ 1 hour from clinic (74% vs 52%, <0.001). There was no statistically significant difference in the number of new HIV diagnoses between home-based and clinic-based testing (1.9 vs 3.4% respectively, p=0.27).

Conclusion: We found home-based HIV testing in Nakivale Refugee Settlement to be feasible with 90% eligible individuals encountered in 3 visits, and acceptable with 75% of eligible individuals encountered participating in HIV testing. Individuals were more willing to test with others home. Home-based testing reached a larger proportion of refugees and those living further from clinic. Home-based HIV testing programs in refugee settlements should be designed to occur during times when multiple people are likely to be present at home at the same time. Moving forward it will be important to assess linkage to care for home-based testers as distance to clinic may impact linkage in the refugee settlement.

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Moytrayee Guha, MPH, Emergency

Implementation of a condom uterine balloon package for uncontrolled postpartum hemorrhage from atonic uterus across 10 medical colleges in India

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Introduction: Postpartum hemorrhage (PPH) is the leading cause of maternal morbidity and mortality worldwide, accounting for approximately 350,000 deaths and 2.6 million disabled women annually. India contributes over 11% of the global burden of PPH deaths. Access to second-line treatment options such as emergency hysterectomy and other surgical interventions is often limited, especially in rural communities across India. PPH-related deaths and disabilities can be avoided if health care providers have access to necessary life-saving knowledge, skills and tools. Over the past eight years, the MGH Division of Global Health and Human Rights has developed and refined the award-winning and highly cost-effective package, Every Second Matters for Mothers and Babies - Uterine Balloon Tamponade (ESM-UBT), designed to arrest uncontrolled PPH after conventional methods have failed. The objective of this study was to assess the impact of ESM-UBT implementation across10 medical colleges in Maharashtra State, India.

Methods: The ESM-UBT package was implemented across 10 medical college hospitals in Maharashtra, India, between January 13 and April 14, 2017. Data were collected via a multi-pronged approach including data card completion, chart reviews, and patient follow-up on potential complications associated with UBT use. Shock class was assigned based on recorded blood pressures and mental status at the time of UBT placement. A woman was said to be in advanced shock if she met criteria for either Class III or Class IV shock. Class III shock was defined as uncontrolled ongoing hemorrhage and a systolic blood pressure (SBP) less than or equal to 90 mmHg and greater than 70 mmHg and/or altered mental status without unconsciousness. Class IV shock was defined as ongoing uncontrolled hemorrhage and SBP less than or equal to 70 mmHg and/or unconsciousness. Women who had alternate causes of PPH – such as cervical tear, uterine rupture, or disseminated intravascular coagulation due to sepsis were excluded.

Results: Seventy-one women had ESM-UBT devices placed between January and July 2017 among the 10 study facilities. Seventy of 71 (98.6%) women had uncontrolled PPH originating from an atonic uterus, and their mean age was 25.7 years. Three of the 70 (4.3%) women underwent hysterectomy despite the placement of an ESM-UBT device. All-cause survival was 97.1% (68/70). Of the 40 (57.1%) women who had normal vital signs or were in mild shock (Class I and II shock), survival was 100%, while the thirty (42.9%) women that were in advanced or end stage shock (Class III and IV shock) had a 93% survival.

Conclusion: The ESM-UBT package is associated with high rates of survival from uncontrolled PPH, especially when placed prior to advanced shock. While data from this proof-of-concept implementation are promising, future studies are needed to evaluate the feasibility and impact of ESM-UBT in lower level health centers in India to inform national scale.

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Jennifer C. Gutierrez, BA, Pediatrics

Improved inter-reader agreement of pediatric chest radiographs for the diagnosis of pneumonia as defined by the World Health Organization

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Introduction: Pneumonia is a leading cause of death among children under 5; per the World Health Organization (WHO) and Maternal and Child Epidemiology Estimation Group, pneumonia was responsible for 920,000 deaths in 2015. Although radiological pneumonia is used in epidemiological studies as a measure of outcome, there is considerable variability in the interpretation of chest radiographs. A standardized method of identifying radiological pneumonia would facilitate the comparison of the results of vaccine trials and epidemiological studies on pneumonia. In 2005, the WHO developed standardized definitions for the interpretation of pediatric chest radiographs along with clarifications and a training module in 2016 to support standardization. In the present study, we sought to assess the impact of the WHO Chest Radiograph in Epidemiological Studies (CRES) training module on the accuracy and consistency of pediatric radiologists' chest radiograph interpretations for pneumonia.

Methods: The one hour training course included an introduction to the WHO definitions of radiological findings and endpoints of pneumonia, which are defined as primary end-point pneumonia (a dense or fluffy opacity of a portion or whole lobe or lung, or a pleural effusion associated with a parenchymal infiltrate), other infiltrate (linear and patchy densities in a lacy pattern, featuring peribronchial thickening and multiple areas of atelectasis, or minor patchy infiltrates not of sufficient magnitude to constitute primary end-point pneumonia), normal, or uninterpretable. An in-depth discussion followed on a series of standardized images until consensus was reached by the radiologists. To measure the impact of the training course on interobserver variability, we administered a test of 150 standardized images before and after the WHO CRES training. Images were provided without clinical information and divided equally before and after the intervention. The results were compared against the consensus readings developed by the WHO CRES Technical Working Group and agreement among the radiologists was measured.
Results: Overall interrater agreement across all test conclusions, measured with the kappa statistic (κ), demonstrate improved agreement, from κ 0.51 (95% CI: 0.40, 0.62) pre-training to κ 0.68 (95% CI: 0.57, 0.80) post-training. Whereas interrater agreement slightly decreased after training for normal (no pathology) from κ 0.59 (95% CI: 0.43, 0.74) pre-training to κ 0.54 (95% CI: 0.35, 0.73) post-training. There was a major improvement in interrater agreement for detecting primary end-point pneumonia (with or without other infiltrate): κ 0.63 (95% CI: 0.49, 0.77) to κ 0.82 (95% CI: 0.71, 0.91), as well as for other infiltrate: κ 0.35 (95% CI: 0.18, 0.53) to κ 0.57 (95% CI: 0.38, 0.76), and uninterpretable image: κ 0.18 (95% CI: could not be calculated) to κ 0.67 (95% CI: could not be calculated). Among the three radiologists tested, the mean pre-training test score was 53 (70.7% correct) and the mean post-training test score was 57.67 (76.9% correct). This improvement in overall diagnostic accuracy, defined as the percentage of chest radiographs that were interpreted correctly, was non-significant, ($t = 0.6705$, $p = 0.57$, $df = 2$).
Conclusion: Using WHO CRES standardized definitions and training, the interpretation of pediatric chest radiographs resulted in a high level of agreement between readers for the definition of primary end-point pneumonia, and moderate agreement for other infiltrate. Overall diagnostic accuracy of readers was improved, and agreement for normal images did not improve. Further research is needed on the reproducibility of results within other specialties of readers.

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Emily M. Hahn, B.S., Athinoula A. Martinos Center for Biomedical Imaging

Cognitive Functioning and Psychotherapy Response in Bipolar Disorder

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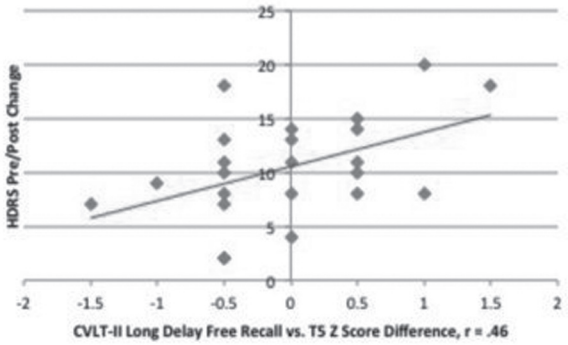
[1]Boston University, Boston, MA, USA, [2]University of Illinois at Chicago, Chicago, IL, USA, [3]Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA and [4]UC Berkeley, Berkeley, CA, USA

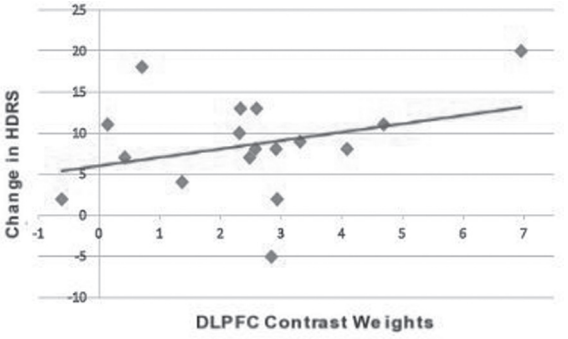
Introduction: Pharmacotherapy is the first line treatment for bipolar disorder but fails to bring most patients to sustained submission. Psychotherapy adjunctive to medication has been shown to prevent relapse and to treat acute depression in bipolar disorder. For example, in the largest multi-site study of bipolar disorder to date, Systematic Treatment Enhancement Program for Bipolar Disorder, Cognitive-behavior therapy, Interpersonal and Social Rhythm therapy as well as family focused therapy were superior to a brief 3-session psychoeducational intervention in reducing symptoms of depression. All three therapies require highly trained clinicians with experience in bipolar disorder that are often not available for patients. On the other hand, the efficacy of supportive psychotherapy for bipolar depression has not yet been investigates. The purpose of this study was to investigate how generic supportive psychotherapy compares to cognitive-behavior therapy for reducing depression in patients with bipolar I disorder who meet DSM-IV criteria for a depressive episode.
Methods: Study participants were 32 depressed individuals with Bipolar I disorder. (16 female; CBT = 17, SP = 15) The interventions, CBT and SP, were randomized across patients, each of which received twenty-two sessions. Before starting psychotherapy, participants completed a battery of neuropsychological tests including the California Verbal Learning Test (CVLT), and selected subtests of the Delis Kaplan Executive Functioning System (DKEFS). Treatment outcome was assessed using the the Hamilton Rating Scale for Depression (HDRS). Participants also completed functional magnetic resonance imaging before treatment. Liinear regression was used to examine BOLD changes across time and conditions using HDRS scores (baseline and change in scores).
Results: Prior to treatment (at baseline), both CBT and SP patients presented with moderate levels of depression (HDRS 17: CBT: $M = 20.9$, $SD = 4.1$, SP: $M = 20.8$, $SD = 2.1$, $p = .94$). Depression symptoms decreased with both CBT and SP groups through the end of treatment (HDRS 17: CBT: $M = 10.9$, $SD = 4.6$, SP: $M = 10.8$, $SD = 5.7$; $p = .58$) and did not show an increase at the three month follow-up (HDRS 17: CBT: $M = 20.9$, $SD = 4.1$, SP: $M = 20.8$, $SD = 2.1$, $p = .94$). Additionally, at follow-up residual manic symptoms were found in both groups (HDRS 17: CBT: $M = 20.9$, $SD = 4.1$, SP: $M = 20.8$, $SD = 2.1$, $p = .94$). Retention of verbal information (CVLT long delay free recall vs. T5 z score difference, $r = .46$) was a predictor of treatment response but not initial ability to learn new information (CVLT-II Trials 1-5, $r = .05$). Another predictor

of treatment response across conditions was inhibition (DKEFS: Stroop, r = -.48). Imaging results revealed activation in the dorsolateral prefrontal cortex (DLPFC) predicted treatment response. Positive associations were found between improvement in HDRS scores and activation in the left dorsolateral prefrontal cortex (BA 9, $p < 0.01$) and the right hippocampus ($p < 0.001$).

Conclusion: The degree of response to supportive psychotherapy was almost identical to that of cognitive behavior therapy, suggesting that depressed individuals with bipolar I disorder do not need specialized psychotherapy. The degree of response depended on declarative verbal memory. Given that content in psychotherapy is expressed verbally, therapists should assess for patient's memory difficulties early on and help patients compensate for such difficulties.



Treatment response measured via HDRS pre and post treatment is predicted by retention (CVLT-II Long Delay Free Recall vs. T5 Z score difference, r = .46)



An estimate of the correlation between HDRS change and DLPFC contrast weight (r = .31, p = .23)

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Haregnesh Haile, Psychiatry

A Pilot Study of Implementation Fidelity in a National School-based Mental Health Program

H. Haile[1], J. Guzman[4,3], C. Lucke[1], F. Peña[3], M. Jellinek[2], K. Canenguez[1] and J. Murphy[1,2]

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Introduction: *Skills for Life* (SFL) is one of the world's largest school-based mental health programs. Since 1998, SFL has been implemented on a national scale in the public elementary schools of Chile. SFL utilizes standardized teacher- and parent-report measures to screen for psychosocial problems in children and then refers those found to be at risk in first grade to an intervention in second grade consisting of 15 workshop sessions. Although a number of recent studies have provided evidence of the positive impact of the intervention on student mental health and academic outcomes, to date there have been no studies evaluating its implementation. Toward this end, the current study explored the relationship between the fidelity of the program's implementation and a number of program outcomes.

Methods: The current study reports on the results of a survey that was emailed to the local team professionals responsible for running the program in 78 elementary schools of more than 2000 participating in SFL. The current study piloted the survey's methods and results in a sample of convenience in preparation for an RCT evaluation of the SFL program in a more rigorously selected sample in the following year. Invitations were sent out via email about halfway through the 2016 school year through a link to the online survey presented through Qualtrics. Surveys gathered information concerning aspects of the workshop's implementation as well as information on support received from colleagues, school staff, and parents, satisfaction of the overall program's execution on a scale of 1 (Very Unsatisfied) to 5 (Very Satisfied), level of agreement on questions about the structure of the program on a scale of 1 (Strongly Disagree) to 5 (Strongly Agree), and demographic information (gender, education, years of experience). The final survey consisted of 82 questions that were administered in Spanish, completed anonymously, and took approximately 20 minutes to complete. Individual survey items were examined and then combined to create scales that were tested for internal reliability. Five scales were created: the Fidelity Scale, the Preparedness Scale, the Personal Satisfaction Scale, the Program Satisfaction Scale, and the Support Scale. Scores on each scale were recoded into dichotomous categorical variables to differentiate lower vs. higher values on each scale to help with interpretation. Chi-square analyses were used to explore the significance of the relationships between lower fidelity of implementation and these other variables.

Results: During the first semester of 2016, there were 48 mental health professionals who completed a survey. Of these 48 surveys received, two were mostly incomplete and two were missing a single item on the Fidelity Scale. Therefore, a total

of 46 cases were used in the analyses for descriptive statistics and chi-square tests while 44 cases were valid for the Fidelity Scale reliability analyses. Participants were primarily female (76.1%), had a professional credential in psychology (71.7%), and had an average of 4.4 years (*SD* = 3.72) of experience implementing SFL. The Fidelity Scale consisted of twenty-nine items and demonstrated high internal reliability (∝=.87) while the other scales for preparedness, personal satisfaction, and program satisfaction consisted of fewer questions (5,6, and 5 items) and also demonstrated moderate to high internal reliability (∝=.71, ∝=.85, ∝=.76, respectively). The Support Scale had low internal reliability (∝ < .55) and was therefore not included in the analyses. Of the 29 items on the Fidelity Scale, 27 were endorsed as "Strongly agree" or "Agree" by 66-98% of all respondents while only two items were less likely to be endorsed positively. These two items pertained to whether the mental health professional had implemented a maximum of 4 workshop groups simultaneously (only 75.0% of respondents said that they strongly agreed or agreed) and whether students newly screened as being at risk in 2nd grade were incorporated into workshops during 2nd semester (only 45.4% of respondents said that they strongly agreed or agreed). In a series of categorical analyses, respondents whose total Fidelity Scale scores were in the lowest 20% were significantly less likely to report high head teacher support (66.7% vs. 94.6 %, χ^2 (45) = 5.8, $p < .05$), high school management support (44.4% vs. 81.1%; χ^2 (45) = 5.0, $p < .05$), high program satisfaction (44.4% vs. 89.2%, χ^2 (45) = 9.2, $p < .01$), or high personal satisfaction (22.2% vs. 94.6%, χ^2 (45) = 24.1, $p < .001$).

Conclusion: The findings of this study demonstrated the feasibility of assessing program fidelity and other aspects of implementation in the Skills for Life program by using an online survey completed by clinical staff. The individual question items that were combined to create the Fidelity Scale as well as the three other scales demonstrated moderate to high internal reliability (∝=.70-.87), and item level descriptive analyses on the Fidelity Scale suggested that the mental health program staff surveyed believe that most areas of the SFL program are implemented faithfully since all but two questions showed high positive ratings. The lack of positive endorsement on these two questions suggested lower fidelity but also areas in which improvements in program implementation might be made. In addition to demonstrating areas for potential improvement in the SFL program, the current findings also suggest that implementation fidelity is associated with other key implementation characteristics like support from head teachers, program management, as well as personal and program satisfaction. These findings provide support for continuing to use an implementation science approach in the RCT evaluation of SFL that is now in progress since it may provide even more insights into which areas of the program are and are not working effectively and where modifications of the program might lead to a more positive program outcome.

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Eduardo Hariton, MDMBA, OB/GYN

The Effects of Clomiphene Citrate (CC) Initiation Day and Dose on Early Pregnancy Outcomes

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Introduction: Since the 1960s, clomiphene citrate (CC) has been used as first line treatment for ovulation induction (OI) in anovulatory women with normal basal levels of endogenous E2. To evaluate the effect (if any) of different CC regimens (dose and/or initiation day) on pregnancy outcomes. Previous studies have shown conflicting data in terms of the effect of cycle start day on cycle outcomes. The objective of this study is to evaluate the effect (if any) of different CC regimens (dose and/or initiation day) on pregnancy outcomes

Methods: Data from 2,453 consecutive CC/intra-uterine insemination (IUI) cycles taking place at Massachusetts General Hospital between 12/2003 and 12/2015 were analyzed. *Outcome Measures*: Clinical (CPR), multiple (MPR), and non-viable (NVPR) pregnancy rates (the latter defined as the rate of biochemical and ectopic pregnancies over all pregnancies), as well as spontaneous abortion (SABR) rates. *Statistics*: A mixed random and fixed effects logistic regression model was fit with a backward elimination algorithm, with CPR, MPR, NVPR, and SABR as dependent variables and CC dose (25, 50, 100, 150 mg), and initiation day (2,3,4, 5 or 6) as primary fixed effect predictors.

Results: 2,453 cycles from 1,051 women were analyzed with a mean (SD) age, BMI, and day-3 (D3) FSH of 33.5 (4.3) years, 24.5 (4.7) kg/m^2, and 7.1 (2.8) IU/L, respectively. As expected, a negative relation of D3 FSH to pregnancy was found ($p<0.01$), with the odds of pregnancy decreasing by 9% (OR=0.91, 95% CI: 0.86-0.98) for every unit increase in FSH. A significant interaction between CC dose and BMI ($p=0.02$) was also found. Specifically, CC dose related positively with CPR in patients with a BMI<25, whereas the opposite was noted among patients with BMI≥25 ($p=0.02$ for interaction). For every 50 mg increase in CC, the odds of pregnancy increased by ~30% in patients with a BMI<25 and decreased by at least 5% in those with BMI≥25 (OR: 1.3 and 0.95, respectively). Initiation day was not found to have a significant effect on CPR. A similar interaction for pregnancy viability ($p<0.001$) indicated that for every 50 mg increase in CC, the odds of viability increased at least 70% in patients with BMI<25 and decreased by at least 55% in patients with a higher BMI (≥30). Neither a change in dose nor in initiation day had an effect on SABR. Interactions of dose with both CC initiation day and D3 FSH (both $p<0.001$) showed that higher doses of CC were generally associated with lower MPR, but the effect was less pronounced

in women with higher day-3 FSH levels and a later CC initiation day. For example, for a 50mg CC increase, the OR of MPR was 0.02 to 0.12 for Day 2 to 5 respectively.
Conclusion: Our findings suggest that the effect of CC dose on CPR is modified by BMI, with increases in dose associated with improved CPR among patients with normal BMI, and worsened ones among those with higher BMIs. A similar modified effect was noted on pregnancy viability. Initiation day was not found to have a significant effect on CPR.

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Eric P. Hazen, MD, Psychiatry

Correlates of Behavioral Difficulties in Patients with Autism Spectrum Disorder Admitted to Inpatient Pediatric Units

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Introduction: Children with Autism Spectrum Disorder (ASD) have higher rates of medical illness than the general pediatric population as well as higher rates of health care utilization, including increased likelihood of medical hospitalization. However, inpatient medical admission is often extremely challenging for individuals with ASD. Existing studies have highlighted some of the challenges involved in the medical care of patients with ASD, such as increased inpatient lengths of stay and decreased satisfaction with care. However, to our knowledge there have been no studies to date examining the predictors of behavioral outcomes associated with the hospitalization of patients with ASD. These outcomes, such as agitation, self-injury, and aggression, are critical to patient and staff safety but there have been no studies characterizing this risk or identifying correlates of behavioral outcomes that might be used to identify patients and circumstances that pose the greatest risk of a behavioral disturbance occurring over the course of an admission.
Methods: Through a retrospective chart review, we identified every patient ages 12-19 years of age with a documented ASD diagnosis admitted to the inpatient pediatrics unit of a large, urban teaching hospital over a five year period. Patients who had clear documentation of diagnosis recorded as "autism", "Autism Spectrum Disorder", Pervasive Developmental Disorder Not Otherwise Specified", or "Asperger's Disorder" were included. Patients who were admitted for primarily psychiatric reasons, such as those awaiting inpatient psychiatric placement, were excluded from the study. We then performed a detailed chart review of each of these admissions. Data gathered included reason for admission, level of pain at the time of admission, co-morbid psychiatric diagnoses, past psychiatric history, history of agitation and self-injurious behavior, history of sensory sensitivities, and degree of intellectual disability. Our primary outcome variable were frequency and severity of episodes of agitation and self-injury that occurred during the hospitalization.
Results: A total of 210 admissions meeting the study criteria were identified. Because some patients had repeat admissions during the study period, a total of 110 unique patients were represented in the sample. Over half of the sample (55.2%) carried at least one co-morbid psychiatric diagnosis, with Attention Deficit/Hyperactivity Disorder being the most common. At least one episode of agitation or self-injury occurred in 27 (12.9%) of the admissions reviewed. To analyze the predictors of adverse outcomes on individuals over multiple inpatient admissions, we employed General Estimating Equations (GEE) logistic regression. Predictors such as 'acute pain,' 'history of agitation,' etc. were categorized as binomial covariates (i.e. presence or absence of event), and measured over patients' admissions for presence or absence of inpatient agitation as our outcome measure. For 39% of the patient population, there were multiple admissions to consider per individual, requiring the use of a semi-parametric approach for repeated measures. The significance of these predictors was determined using univariable analysis. There was a statistically significant association between agitation or self-injury during the admission and the following factors: past history of agitation or aggression (Odds Ratio= 12.4.0, $p<0.001$), history of self-injurious behavior (OR=8.9, $p<0.001$), documented history of sensory sensitivities (OR=4.1, $p<0.003$), and history of past psychiatric hospitalization ((OR=4.0, $p<0.003$). There was no association between agitation and intellectual disability or the presence of acute pain upon admission.
Conclusion: While the majority of adolescents with ASD admitted to pediatric medical units will not have episodes of agitation or self-injury during the admission, there is a significant subset of patients who will experience these difficulties. We found that agitation and self-injury occurred more commonly in patients with a past history of these behaviors as well as in those with a history of psychiatric hospitalization and sensory sensitivities. Agitation during admission was not associated with intellectual disability or the presence of acute pain in our sample. Further research is needed to identify risk factors for patients with ASD who may have behavioral difficulties during medical hospitalization. A better understanding of these risk factors would allow for better screening at the time of admission to identify and intervene with high risk patients to reduce their risk of agitation and improve the quality of their care.

Associations with Agitation (Chi Square Method)

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Samantha N. Hellberg, Bachelor of Arts, Psychiatry

Utilizing a Network Approach to Examine the Structure of the Weighted Mental Disorder Symptom Network and its Relation to Comorbidity

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Introduction: Mental disorders can be conceptualized and studied as overlapping networks of mutually reinforcing symptoms. Researchers have previously used diagnostic manuals to estimate the global structure of the mental disorder symptom network. However, these studies estimated *unweighted* networks, in which links between symptoms are only either present or absent. Here, we use the International Classification of Diseases (ICD) to assess the structure of the *weighted* symptom network, accounting for differences in the strength of relationship between symptoms. We then assessed whether proximity of disorders in this network was associated with their comorbidity rates.
Methods: The R package igraph was used to estimate the network, with nodes representing the 588 symptoms of the ICD, linked by an edge if they appear together in a disorder. Edge weights reflected the number of times symptoms co-occurred across 150 ICD disorders. We compared the ICD network to networks randomly generated using Erdos-Renyi and degree-preserved randomization to determine if the observed structure could be expected to arise by chance. We then examined if average shortest path length between disorders was associated with the comorbidity rate of those disorders for 8 well-studied ICD disorders (Slade & Watson, 2006).
Results: Large edge weights occurred significantly more frequently in the ICD than in either comparison network. Strongest edges were among insomnia, decreased energy, difficulty concentrating, and lost confidence. Weighted distance between disorders was associated with comorbidity rates, $r = -.44$, $p = .018$ (cf. $r = -.39$ for unweighted; Tio et al., 2016).
Conclusion: Symptoms co-occur across disorders more than would be expected by chance, suggesting these symptoms may be strongly connected. Incorporating this strength of connection, weighted distance between disorders was modestly more strongly associated with comorbidity than was unweighted distance. Our findings suggest that this weighted symptom network provides meaningful information about the relationships among symptoms and, thus, the broader system of psychopathology and supports further clinical study on the influence of symptoms (e.g., insomnia) on comorbidity.

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Daniel Henderson, Medicine - Primary Care

Diffusion of a Continuity of Care Innovation: Examining the Impact and Spread of Continuity Visits Among PCPs

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Introduction: Continuity of care across settings, or lack thereof, is a key driver of the patient experience. Furthermore, the issue of preventable readmissions has created high stakes for hospitals to manage transitions of care and to enhance continuity. Primary care physicians (PCPs) play a crucial role, as the most common anchor of patients' relationships with the hospital. Increasingly, this role is being recognized and formally supported, creating innovation opportunities. We sought to study one such innovation: the Continuity Visit program at MGH. We studied trends in PCP us of the program, looking at rates of participation and patterns of diffusion of innovation. We also sought to analyze downstream impact on follow-up visits, a critical defense against readmission. Here we present the results of our analysis and lessons for future innovation.
Methods: In response to patient and physician dissatisfaction with perceived deficits in continuity of care, the MGPO convened a task force to examine the issue, clarify expectations, and identify solutions to enhance continuity amidst shifts in healthcare delivery. From the task force came the creation of the Continuous Care Initiative (CCI) in 2010. The CCI developed a portfolio of analyses and interventions, most notably, the Continuity Visit Program, by which the MGPO sought to support clinicians for visiting their patients when hospitalized. By formalizing the practice of making these brief visits with patients and their clinicians and supporting the time cost of such visits through a modest stipend, continuity visits offered an opportunity to bridge the divide between ongoing and acute care. In 2012 continuity visits began and were followed in 2014 by discharge continuity visits, which carried a higher stipend to PCPs who visited their patients in the days before discharge and communicated with the inpatient team about discharge planning. Despite the clinical and financial appeal, these visits were under-utilized early on. To study rates of participation and trends in uptake, we obtained billing data for admissions of patients with an established MGH PCP beginning in 2014. We tracked rates of continuity and discharge continuity visits per admission over time, and between practices and individual PCPs. We also captured inpatient billing data to identify PCPs who saw their admitted patients as attending of record. We obtained data of subsequent outpatient follow-up visits for 45 days

after discharge. From this data, we examined the effect of continuity on follow-up visits using multivariate logistic regression. To better understand uptake and barriers to participation, we surveyed PCPs about the program. We then conducted outreach interventions to raise awareness, address barriers and increase participation.
Results: Out of 41 survey respondents (a 66% response rate), key barriers were lack of time, lack of understanding of the program and lack of timely notification of discharge. At that time, the rate of on-campus PCPs making continuity visits was 8% and less than 1% for discharge continuity visits. After the interventions, which began in late 2015 and included informational emails, presentations at meetings, and face-to-face teaching of individual PCPs, the rate increased to 18.0% for continuity visits and 5.0% for discharge continuity visits. The proportion of PCPs making continuity visits increased from 48.6% to 65.8% and from 8.1% to 36.8% for discharge continuity visits. We noted evidence of social spread of continuity participation and increased uptake by PCPs who had more contact with our outreach interventions. To assess the impact on follow-up, we analyzed 6,359 hospital stays of patients with established MGH PCPs who were discharged from medicine services between 2014-2016. Of these, continuity contacts (defined as the PCP making a continuity visit of either type, or serving as the patient's attending of record) occurred on 32.0% of hospitalizations. After discharge, 62.3% of patients had one or more follow-up visits within 30 days and 29.3% had a visit with their own PCP. In a hierarchical logistic regression model controlling for age, length of stay, comorbidity, gender, PCP practice, and discharge destination, continuity contact was associated with a 53% greater likelihood of follow-up with a patient's own PCP (OR 1.53, 95% CI 1.34-1.75, $p<0.001$).
Conclusion: Our analysis identified important barriers to adoption of the program and saw increases in adoption when these barriers were addressed. Further, the intensity of communications to PCPs, as well as the degree of adoption among close peers, were loosely associated with greater participation. The findings highlight two important points: First, even small change is hard and low-intensity communication, such as broadcast-style email, is insufficient to drive adoption. Second, the spread of the program followed classic patterns of diffusion of innovation, with typical groups of earlier and later adopters, and diffusion along lines of rich interaction and communication. Our findings also identified a previously expected but unproven association between continuity contact and own-PCP follow-up care. This asscciation offers a plausible pathway by which continuity may impact patient satisfaction, care quality, and readmission prevention. While it may be possible that this association reflects another aspect of the patient-physician dynamic (e.g. that PCPs generally see their sicker patients during and after hospitalization) we consider this to be a valuable association irrespective of causality. As participation in the continuity program grows, we hope to explore clinical and care process outcomes to evaluate other downstream benefits of continuity.

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Clayton Hess, MD, Radiation Oncology

Inter-Institutional Sharing of Electronic Medical Records Enhances Reporting of Prospective Pediatric Oncology Research

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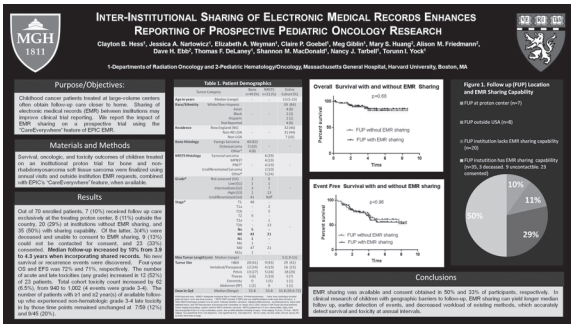
Introduction: Childhood cancer patients treated at large-volume centers often obtain follow-up care closer to home. Sharing of electronic medical records (EMR) between institutions may improve clinical trial reporting. We report the impact of EMR sharing on a prospective trial using the "CareEverywhere" feature of EPIC EMR.
Methods: Survival, oncologic, and toxicity outcomes of children treated on an institutional proton trial for bone and non-rhabdomyosarcoma soft tissue sarcoma were finalized using annual visits and outside institution EMR requests, combined with EPIC's "CareEverywhere" feature, when available.
Results: Out of 70 enrolled patients, 7 (10%) received follow up care exclusively at the treating proton center, 8 (11%) outside the country, 20 (29%) at institutions without EMR sharing, and 35 (50%) with sharing capability. Of the latter, 3(4%) were deceased and unable to consent, 9 (13%) could not be contacted for consent, and 23 (33%) consented. Median follow-up increased by 10% from 3.9 to 4.3 years. No new survival or recurrence events were discovered. Four-year OS and EFS was 72% and 71%, respectively. The number of acute and late toxicities (any grade) increased in 12 (52%) of 23 patients. Total cohort toxicity count increased by 62 (6.5%), from 940 to 1,002 (4 events were grade 3-4). The number of patients with ≥1 and ≥2 year(s) of available follow-up who experienced non-hematologic grade 3-4 late toxicity in by those time points remained unchanged at 7/59 (12%) and 9/45 (20%).
Conclusion: EMR sharing was available and consent obtained in 50% and 33% of participants, respectively. In clinical research of children with geographic barriers to follow-up, EMR sharing can yield longer median follow up, earlier detection of events, and decreased workload of existing methods, which accurately detect survival and toxicity at annual intervals



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Thomas F. Heyne, MD, Medicine

Massachusetts General Hospital: Sonography in internal medicine, baseline assessment (MGH SIMBA)

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Introduction: We stand on the brink of a revolution in clinical care. For decades, ultrasound machines have been used successfully by technologists and radiologists, but increasingly they are coming to the patient's bedside. As ultrasound machines have become more portable and less expensive, clinicians are increasingly using them as they might a stethoscope. In a matter of seconds to minutes, a physician with ultrasound can diagnose heart failure, pneumonia, leg clots, gallstones, and other diseases. Within emergency departments, Point-of-Care Ultrasound (POCUS) has been shown to improve patient outcomes, reduce complications, increase patient satisfaction, and facilitate faster and more accurate diagnoses. POCUS revolutionized Emergency Medicine after it was adopted by that specialty, and many experts predict that it will soon transform Internal Medicine (IM) as well. Some programs, such as UCSF, OSHU, and Emory, have begun to train IM physicians in POCUS. Prior to this study, however, it remained unclear whether MGH IM residents and faculty desired or valued such training. The study aimed to assess the (1) interest in, (2) opinions about, and (3) experience in POCUS in MGH IM residents and inpatient faculty.

Methods: Two separate anonymous online needs assessment surveys were designed and emailed to two groups: the MGH IM residents and the MGH IM inpatient clinical faculty (hospitalists and Core Educators). 95% confidence intervals were calculated for categorical data, and median/mode were calculated for ordinal data. The MGH IRB deemed the study exempt.

Results: Overall, both residents and faculty showed significant interest in POCUS training and high regard for the benefits of POCUS. A total of 83/184 (45%) of residents responded, and 43/79 of faculty (54%, with 33/62 hospitalists and 10/16 Core Educators) responded. Among resident respondents, 99% (n=79) thought that POCUS training should be a formal part of IM residency training. 96% (n=77) desired to sign up for an ultrasound elective (not currently offered), and 96% wanted POCUS training during their outpatient rotations. 80% of respondents felt that their residency training was lacking due to lack of POCUS training. Residents showed high esteem for POCUS: 92% (n=73) thought it would improve patient care, 84% thought it would improve patient safety, and 88% thought it would improve efficiency. Similarly, 86% thought that POCUS would assist in managing "Code Blue" events. Finally, residents admitted to using POCUS frequently in the hospital, even when they felt incompetent to do so. For example, 31% of responding residents said that they used POCUS for assessing IVC volume (95% CI: [0.21, 0.41]), but only 6% felt competent to do so (95% CI: [0.01, 0.11]). Similarly, 20% of respondents use POCUS to assess LV function (95% CI: [0.12, 0.29]), but only 1% felt confident to do so (95% CI: [-0.01, -0.03]). Faculty responses showed similar enthusiasm and lack of diagnostic POCUS training. 90% of respondents (n=37) wanted more diagnostic POCUS training; 95% thought it would improve their educational skills; 82% thought it would improve patient care and patient safety; and 80% thought it would improve care efficiency. 83% (n=33) of faculty respondents expressed interest in a POCUS credentialing pathway. The faculty also reported a discrepancy between using POCUS and feeling competent to do so. For example, 70% of faculty respondents report using POCUS to look for ascites, but only 56% feel competent to do so (95% CI: [0.41, 0.71]). Similarly, 12% of faculty respondents report scanning the bladder, but only 2% feel competent to so (95% CI: [-0.02, 0.07]. Responses in all categories were similar between both hospitalists and Core Educator faculty. Among the major barriers to POCUS use, both residents and faculty most frequently selected insufficient number of machines and training as the two major barriers. Among the possible POCUS applications for internists, both residents and faculty believed the five most important applications to be: ascites assessment, peripheral IV placement, volume status assessment using the inferior vena cava (IVC), diagnosis of pleural effusion, and evaluation of left ventricular function.

Conclusion: Within our institution, IM residents and inpatient faculty strongly desire more POCUS training and think it will improve patient care, patient safety, and hospital efficiency. Given that the groups surveyed--IM residents and inpatient faculty--together care for the bulk of MGH inpatients, their opinions and reported practices are significant. In particular, we discovered a discordance between self-reported POCUS use and competency. Currently, numerous residents (and several faculty) are using POCUS to make clinical decisions, even when they feel incompetent to do so. This incompetence could be considered a patient safety issue. Thus, not surprisingly, both faculty and residents showed strong interest in additional training opportunities, including weekend workshops, an elective, and an official credentialing pathway. Finally, both groups of IM clinicians perceive lack of training and lack of machines as the two major barriers to POCUS use. Taken together, the results provide a compelling case for POCUS training for IM residents and faculty, for the sake of patient care and safety.

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Jaclyn Hirschey, BA, Dermatology

Evaluating a mobile application for atrial fibrillation using qualitative methods: An exploratory pilot study

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Introduction: Atrial fibrillation (AFib) affects nearly 6.1million people in the US. It is characterized by heart palpitations, dizziness, and dyspnea, and associated with increased health care costs, and reduced quality of life. Additionally, individuals with AFib have a 5-fold increased risk of stroke. To manage stroke risk, more than half of individuals with AFib are prescribed a non-vitamin K antagonist oral anticoagulant (NOAC). NOACs have several advantages over older anticoagulant medications (e.g. warfarin), however, medication non-adherence continues to be a challenge. More than half of individuals on a NOAC do not meet an adherence threshold of 80%, putting them at an increased risk for thrombus formation. The need for strict treatment adherence, coupled with distressing symptoms, and disease complexity, make patient self-care difficult. The goal of this study is to evaluate the perceived usability and usefulness of a mobile app, called AFib Connect, that was designed to support self-care and treatment adherence among AFib patients prescribed NOACs. Prior studies have shown how mobile apps that target self-care and treatment adherence can provide critical support to patients managing chronic conditions, however this study is the first we are aware of that specifically examines how these tools can be used for AFib.
Methods: This exploratory study used qualitative methods that combined naturalistic app use, semi-structured interviews and surveys to understand patient perceptions of the app. A purposeful sample of 12 adults in the Boston area, diagnosed with non-valvular AFib, and taking NOACs to manage stroke risk were selected to participate. A 4 week, 5 visit study design gave participants the opportunity to use the app at home and provide detailed feedback on a few app features each week. An a priori coding framework was developed from interview questions, and emergent codes were inductively derived from transcripts. At study completion, codes from each interview were compared and organized into themes to derive final results. Supplementary data was collected by custom surveys. At study enrollment, information on participant demographics and technology use was collected and at closeout, patient satisfaction and app usability was measured. Demographic, tech use, patient satisfaction and usability characteristics were summarized for all 12 participants.
Results: Twelve individuals with an mean age of 59 years completed the study. All participants somewhat or strongly agreed that the app was easy to use, and 92% (11/12) reported being satisfied or very satisfied with the app. Participant feedback identified changes that may improve app usefulness and usability. Areas of usability improvement were organized by three themes: app navigation; clarity of app instructions and design intent; and software bugs. Perceptions of app usefulness were grouped by three key variables: core needs of the patient segment; patient workflow while managing AFib; and the app's ability to support the patient though each stage of their condition. While the target population of this study was any non-valvular AFib patient prescribed a NOAC, our data identified a few patient segments within this group: newly diagnosed patients vs. those managing AFib for an extended period; and patients who are otherwise healthy vs. those with multiple comorbidities. Since participants in our sample had been managing AFib for an average of 5.67 years all expressed the app would have been more useful when they were first diagnosed, and still learning about AFib. Feedback also indicated that how well the designed path through the app matches patients' natural workflow when they seek AFib information or track symptoms impacts its overall usefulness. Participants also discussed how their needs now differ greatly from when they were first diagnosed. Similarly, we expect that as an AFib patient gets older, or experiences an improvement or deterioration in their condition, that their health priorities and needs will also change. To build more useful and usable tools for AFib, it's essential to holistically examine the context in which patients experience the condition. We should evaluate if the app meets the key needs of the target population, fits into their natural workflow, and if it can continue to support them through each stage of the condition.

Conclusion: The results of this exploratory study suggest that mobile tools that target self-care and treatment adherence can be helpful to AFib patients, particularly those who are newly diagnosed. Additionally, participant feedback provided rich insight into the varied needs of AFib patients, which may improve the design and targeting of the intervention. The value of incorporating patient perspectives during the early stages of intervention design is supported by a growing body of research, and the benefits of qualitative methods for gaining insight into the acceptability of health apps are well documented. Yet, it is still rare for medical studies to qualitatively examine patient perceptions of a treatment at an early stage, or at all, prior to implementation. This often leads to less than optimal, or negative outcomes for patients who receive the intervention. Results from this study we hope will help clinicians and researchers in the field of AFib care learn from our research and design insights, and ultimately build better tools for patients with this burdensome condition. Additional studies evaluating the app over a longer period, and including a larger, more diverse sample, will be helpful for understanding whether it is more broadly useful and effective in supporting self-care and med adherence.

Table 1: Summary of participant characteristics

Characteristics (n=12)	Mean (SD) or n (%)
Age (years)	59.25 (7.78)
Time since AFib diagnosis (years)	5.67 (4.54)
Gender	
Male	7 (58.33%)
Race	
Caucasian	12 (100%)

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Barbora Hoskova, BA, Psychiatry

A Prospective Open-Label Trial of Extended-Release Liquid Methylphenidate for the Treatment of Attention Deficit/Hyperactivity Disorder in Adults with High-Functioning Autism Spectrum Disorder: An Interim Analysis

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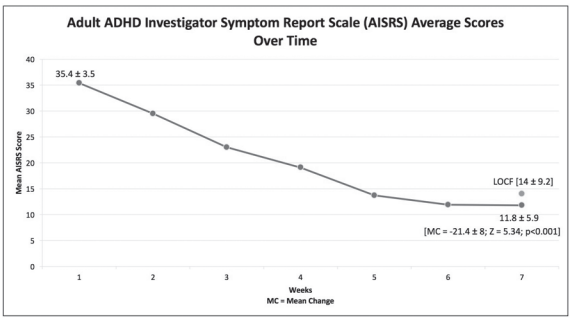
Introduction: Treating ADHD comorbid with ASD could improve morbidity and impairment in autistic individuals; however, lower tolerability to psychotropic medications, used to treat ADHD, has been noted in ASD populations. The purpose of this interim analysis of the ongoing six-week trial was to assess the tolerability and efficacy of extended-release liquid methylphenidate hydrochloride (brand name Quillivant) for the treatment of ADHD in adults with high-functioning ASD.
Methods: Data from 11 adults, ages 19-28, with high-functioning ASD comorbid with significantly severe ADHD was collected during a six-week clinical trial. During the initial three-week dose optimization phase medication was titrated up to the targeted daily dosage. Week 3 and onwards, subjects were maintained on maximum achieved dose with a one-time option to decrease to the next lowest available dose per clinician judgment. Efficacy was assessed utilizing clinician-rated measures (Adult ADHD Investigator Symptom Report Scale [AISRS] and Clinical Global Impression Scale [CGI]) and a self-rated measure (Adult ADHD Self-Report Scale [ASRS]). The primary outcome criteria for response was ≥30% reduction in AISRS total score and CGI-ADHD-Improvement score ≤2. Tolerability was assessed through safety measures including vital signs and treatment emergent adverse events.
Results: Results show significant improvement in AISRS scores with a significant mean reduction of 21.4±8 from baseline (35.4±3.5) to endpoint (11.8±5.9). Overall, 82% of subjects met the primary outcome criteria for response. Similarly, significant improvement was noted in the self-rated measure of ADHD severity (baseline: 43±6.7; endpoint: 33±10; mean reduction: 9±11). The medication was well-tolerated in subjects. Adverse events were experienced by 9/11 subjects (82%). Reported adverse events were transient and mild to moderate. Most frequently noted adverse events (>10%) were headaches (45%), insomnia (27%), decreased appetite (27%), and anxiety (18%). One subject terminated due to treatment limiting adverse events (headaches, palpitations, jaw pain, and insomnia).
Conclusion: Our findings suggest that extended-release MPH formulation is very effective and well-tolerated in the treatment of ADHD symptoms comorbid with high-functioning ASD.

Demographic and Clinical Characteristics

Demographic Characteristics		
Participants (total)		*11*
Gender (men)		*9 (82%)*
Age (years)	*Mean±SD*	*24±3*
	Range	*19-28*
Clinical Characteristics		
Full Scale IQ	*Mean±SD*	*117±16*
	Range	*99-144*
Diagnoses (DSM-V)		
Autism Spectrum Disorder		*11 (100%)*
ADHD-Combined Type		*7 (64%)*
ADHD-Inattentive Type		*4 (36%)*
Baseline Severity		
ASD (SRS-2 Adult Self-Report Score)		*105±25*
ADHD (AISRS Clinician-Rated Score)		*35±3.5*
Global Assessment of Functioning	*Mean±SD*	*56±2*
	Range	*53-60*
Adjunctive Medications		
SSRI/SNRI/DNA		*6 (55%)*
Atypical Antipsychotic		*1 (9%)*



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Esther Howe, BA, Psychiatry

Feasibility of an Automated System Counselor for Survivors of Sexual Assault

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Introduction: Sexual assault (SA) is common and costly to individuals and society, and increases risk of mental health disorders. Stigma and cost of care discourage survivors from seeking help. Norms profiling survivors as heterosexual, cisgendered women dissuade LGBTQIA+ individuals and men from accessing care. Because individuals prefer disclosing sensitive information online rather than in-person, online systems—like instant messaging and chatbots—for counseling may bypass concerns about stigma. These systems' anonymity may increase disclosure and decrease impression management, the process by which individuals attempt to influence others' perceptions. Their low cost may expand reach of care. There are no known evidence-based chat platforms for SA survivors Objective: To examine feasibility of a chat platform with peer and automated system (chatbot) counseling interfaces to provide cognitive reappraisals (a Cognitive Behavioral Therapy technique) to survivors.

Methods: Participants are English-speaking, U.S.-based survivors, 18+ years old. Participants are told they will be randomized to chat with a peer or automated system counselor 5 times over 2 weeks. In reality, all participants chat with a peer counselor. Chats employ a modified-for-context evidence-based cognitive reappraisal script developed by Koko, a company offering emotional support services via social networks. Baseline Measures: The Brief Fear of Negative Evaluation Scale and self-disclosure items from the International Personality Item Pool. Post-chat Measures: Questions from the Client Satisfaction Questionnaire (CSQ), Self-Reported Attitudes Toward Agent, and the Working Alliance Inventory. Hypotheses: 1) Online chatting and automated systems will be acceptable and feasible means of delivering cognitive reappraisals to survivors. 2) High impression management (IM≥25) and low self disclosure (SD≤45) will be associated with preference for an automated system. 3) IM and SD will separately moderate the relationship between counselor assignment and participant satisfaction.

Results: Ten participants have completed the study. Recruitment is ongoing. We will enroll 50+ participants by 10/2017. To date, 70% of participants completed all chats within 24 hours of enrollment and 60% indicated a pre-chat preference for an automated system, suggesting acceptability of the concept. The post-chat CSQ mean total score of 3.98 on a 5-point likert scale (1=Poor; 5=Excellent) suggests platform acceptability. Of the 50% reporting high IM, 60% indicated preference for an automated system. Of the 30% reporting low SD, 33% reported preference for an automated system. At recruitment completion, ANOVA analyses will elucidate relationships between IM, SD, and counselor assignment. Correlation and linear regression analyses will show any moderating effect of IM and SD on the relationship between counselor assignment and participant satisfaction.

Conclusion: Preliminary results suggest acceptability and feasibility of cognitive reappraisals via chat for survivors, and of the automated system concept. Final results will explore relationships between SD, IM, counselor type, and participant satisfaction to inform the development of new platforms for survivors.

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Yichuan G. Hsieh, PhD, Medicine - Laboratory of Computer Science

Researcher Feedback Regarding the Use of the Partners Research Portal for Study Recruitment

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Introduction: The Partners research portal (https://clinicaltrials.partners.org/) was developed to harmonize public-facing study recruitment efforts. The design of the site, based on crowd-funding platforms which have a similar need to attract and efficiently inform users, was guided by iterative conversations and feedback from patients and researchers in the Partners community. Advanced search, a prominent project image and key project details are highlighted to allow visitors to scan projects that may be of interest to them. Since its launch on October 5, 2016, more than 56,000 unique visitors have visited the site and more than 36,000 visitors have contacted study teams across the 423 published studies.[1] In this review, we present a summary of survey feedback from the researcher community about their experience using the website as a recruitment aide.
[1] Usage data as of June 30, 2017.

Methods: This project was categorized under quality improvement and exempt from IRB review. Teams with published studies in February 2017 were asked to offer their feedback regarding their experience using the site. Specifically, we were interested in characterizing our impression that studies were having difficulty responding to volunteer inquiries within the recommended two business days. Surveys were implemented in REDCap and invitations with the survey link were emailed to the study contacts. A reminder email was sent two weeks after the initial invitation. The questionnaire included five multiple-choice questions and one free-text question (Figure 1). Descriptive analysis was used summarize the findings.

Results: During the two-month data collection period, 139 surveys were received from 266 studies (response rate 52%). Twenty-two percent (n=31) of respondents reported that they did not respond to all volunteer inquiries. When asked about how many inquires they felt comfortable handling daily, most respondents (69%, n=94) reported they were only able to handle one to ten inquiries daily, 12% (n=16) reported that they could handle up to 20 and an additional 16% (n=23) reported that they could address more than 20 or any number of requests a day. In terms of response time, 60% (n=84) stated that they were able to do so within two business days. Forty percent (n=55) required more than two business days, of which eight teams needed more than five business days. Overall, almost all of the respondents (n=126, 92%) indicated that they did not receive more inquires than their study team could comfortably field. For those studies that received volunteer inquiries, more than half (n=71, 51%) reported that they were able to enroll volunteers. When asked about their experience using the research portal as a recruitment tool, most of survey respondents indicated that the service is helpful and highlighted the ease of use for potential volunteers. “Very well organized and designed. I liked being able to select which inquiries were enrolled, ineligible, archived etc.” Several teams complained about receiving interest from ineligible subjects, and many requested the ability to customize their interest form. A number of users reported difficulty in tracking responses and suggested that “it would be helpful to be able to manage the responses and indicate who we had reached out to and who still need to be contacted.” A few other features for future improvement were also suggested, including the ability to export volunteer data and to send “email templates” that “we could...send to the inquirer electronically. This may help... studies that do get a lot of inquiries daily.”

Conclusion: We were pleased that more than half of the survey respondents were able to enroll participants through the research portal, but the large number of teams that were not able to respond to volunteer inquiries within the recommended two business days, and the 22% of respondents who did not follow up on all volunteer inquiries, leaves much room for improvement. Any delay in replies—and not replying—to volunteer inquiries jeopardizes the mission of the research portal as a useful resource and may reflect poorly on the Partners research community more broadly. Study teams are ultimately responsible for follow up communications with potential participants, but there are clear improvements that can be made to the research portal to support timely follow up. In response to feedback, we are expanding the project contact forms to allow customization and are designing more sophisticated roster tools to support volunteer tracking, call documentation and canned electronic messaging. Moreover, while we plan to continue to regularly engage the research community and public to collect formal feedback, we anticipate that these tools will also allow better quantitative tracking of research portal use over time to complement self-reported experiences and ad-hoc feedback.

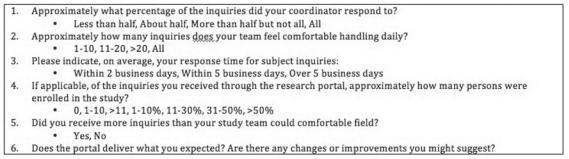
1. Approximately what percentage of the inquiries did your coordinator respond to?
   - Less than half, About half, More than half but not all, All
2. Approximately how many inquiries does your team feel comfortable handling daily?
   - 1-10, 11-20, >20, All
3. Please indicate, on average, your response time for subject inquiries:
   - Within 2 business days, Within 5 business days, Over 5 business days
4. If applicable, of the inquiries you received through the research portal, approximately how many persons were enrolled in the study?
   - 0, 1-10, >11, 1-10%, 11-30%, 31-50%, >50%
5. Did you receive more inquiries than your study team could comfortable field?
   - Yes, No
6. Does the portal deliver what you expected? Are there any changes or improvements you might suggest?

Figure 1. Research Questionnaire

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Ya-Ching Hung, Surgery

Reducing Road Traffic Death: Where Should We Focus Global Health Initiatives?

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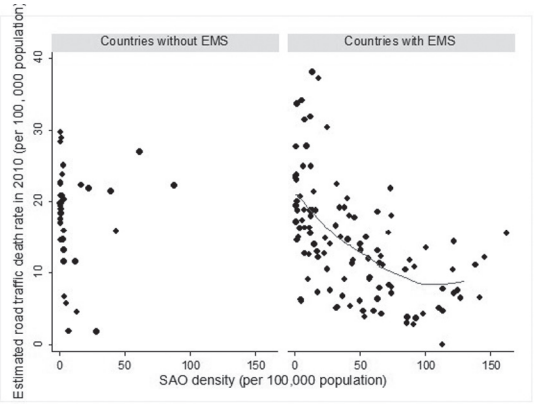
Introduction: Road traffic death (RTD) is a major global health concern. Current global surgery initiatives focus on developing a surgical workforce to address RTD. However, it is unclear whether this approach would be helpful in all countries, as patients in low resource countries may not be able to reach hospitals in a timely enough fashion to receive life-saving trauma care.
Methods: Estimated RTDs were obtained from the Global Status Report on Road Safety 2013 (GSRRS 2013) which estimated the RTD rate in 2010 (RTD 2010). The classification of Emergency Medical Services (EMS) was defined by GSRRS 2009. The density of surgeons, obstetricians and anesthesiologists (SAO density) and 2010 income classification were accessed from the World Bank. Multivariable regression analysis was performed adjusting for different trauma system characteristics in different countries and income levels. Sensitivity analysis was performed using the RTD 2013 or the all-cause injury mortality rate as dependent variables.
Results: On adjusted analysis, SAO density was not associated with changes in the RTD 2010 rate in countries without EMS *(p*=0.50). However, for countries with EMS, each increase in SAO density per 100,000 population decreased road traffic death rates by 0.079 per 100,000 population (p<0.001). Income was the only factor resulting in reduced mortality rates. Similar results were found in the sensitivity analysis.
Conclusion: Increases in surgical workforce reduces RTDs only when EMS exist. In countries without EMS, investment in prehospital systems and training non-clinical personnel should be prioritized. Global surgical initiatives should also focus on bringing a non-physician workforce to developing countries.



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Ya-Ching Hung, Surgery - Pediatric

Unexpected Outcomes of Circumcision: A Population Analysis

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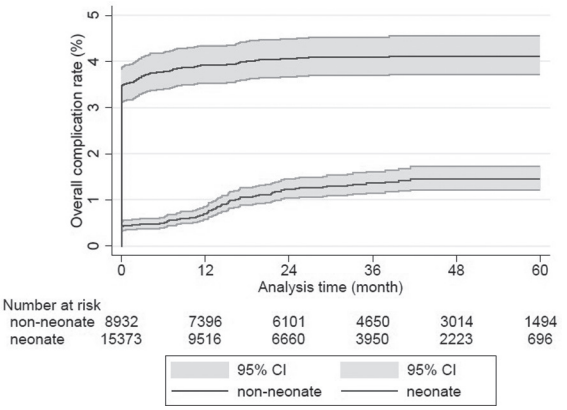
Introduction: Circumcision is widely accepted for newborns in the United States. However, circumcision carries a risk of complication, the rates of which are not well described.
Methods: Retrospective longitudinal analysis of the California Office of Statewide Health Planning and Development patient discharge database (OSHPD) was performed for the years 2005 to 2010. Circumcised patients under the age 5 years were analysed. Using ICD-9 and CPT codes, we abstracted immediate and 5-year overall complications. Multivariate regression was performed to determine the risk of immediate complications, adjusting for the demographics of the patients.
Results: A total of 24,305 children were analysed. Immediate complication rates were 1.5%, with 1.1 % requiring surgical repair while the additional 0.4% had haemorrhage or infection that did not require repeat surgery. 5- year complication rate

was 4.1%, with 5-year re-operation rate of 3.9%. 5-year complications were higher in non-neonates than neonates (4.1% and 1.5% respectively), in outpatients than in-patients (3.9% and 1.6% respectively) and varied with different insurance types (all p<0.001). On adjusted analysis, non-neonates (OR 7.96) and inpatient (OR 2.04) circumcision had significantly higher risks of 5-year complications. (all p<0.001).

Conclusion: The complication rate for male circumcision is 4.1% and is higher than previously reported. The majority of these patients require a second operation. Clinicians should include a discussion of these risks when counselling parents about circumcision.



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Aura M. Hurtado Puerto, M. D., Psychiatry

Safety of Cerebellar Theta Burst Stimulation

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Introduction: The cerebellum is an intricate neural structure with a regulatory homeostatic impact on circuits involving motor and non-motor functions. In recent years, there has been an increasing interest in the neuromodulation of the cerebellum with Transcranial Magnetic Stimulation (TMS) for therapeutic and basic science applications. Theta Burst Stimulation (TBS) is an efficient and powerful TMS protocol, able to induce longer-lasting effects with shorter stimulation times compared to traditional TMS. As a more intensive protocol, there is hypothetically, an increased risk of adverse events (seizures, pain, etc.) when applying TBS. The safety of TBS over the cerebellum has not been thoroughly explored in the literature, even if common variables (scalp to target depth, histology, excitability, etc.), that traditionally define TMS safety and efficacy, are different for this specific application. Given these particularities, we aimed at evaluating the safety and risk for adverse events with current parameters of cerebellar TBS and highlight issues to consider.

Methods: Through PubMed, we performed a systematic literature review of empirical studies applying cerebellar TBS, documented the stimulation parameters used and calculated the risk for adverse events.

Results: Forty-nine articles of cerebellar TBS were identified, where over 2500 cerebellar TBS sessions were carried out in over 900 subjects. There were no serious adverse events reported. 27 subjects experienced non-serious adverse events and 5 were subsequently withdrawn from studies. In decreasing frequency, reported adverse events included: local pain or discomfort over the stimulation area, discomfort due to cervical muscle contraction, headache, drowsiness, nausea, lightheadedness and distress due to anticipation of the stimulation session. We calculated a crude risk per person of 3.8%, by using only the population of the studies that accounted for adverse events. Stimulation parameters are often translated from those used over cerebral cortical areas, and have recently become more intense. Adverse events related to muscle discomfort were most frequently reported in studies, where a higher relative stimulation dose was used.

Conclusion: No serious adverse events have been reported for cerebellar TBS. There is no substantial evidence of a safe maximal-efficacy stimulation dose in humans. Translation of cortical excitability and SIs from the cerebral cortex to cerebellar regions has no guaranteed equivalence. Further research for the stimulation dose in cerebellar TBS is warranted, along with consistent report of adverse events.

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Rocio Hurtado, Medicine - Infectious Diseases

Cause of Death among Multidrug resistant Tuberculosis patients enrolled in a National MDR-TB Treatment Program in Ethiopia.

R. Hurtado[1,4], D. Meressa[3], J. Andrews[5], K. Abato[3], M. Tadesse[3], S. Hagos[3], T. Daniel[3], A. Ashenafi[3], G. Desta[3] and A.E. Goldfeld[2,4]

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Introduction: Multidrug resistant tuberculosis (MDR-TB) treatment in Africa is associated with the highest mortality of any region among patients who receive therapy globally. Though HIV co-infection and severe malnutrition have been identified as risk factors predictive of death in several cohorts, little is known regarding the cause of death among MDR-TB patients enrolled in a treatment program in the African context. In 2009, the Global Health Committee, in partnership with the Federal Ministry of Health of Ethiopia, initiated the first cohort of MDRTB patients in the country on treatment for MDRTB, as there was no prior mechanism for accessing treatment in Ethiopia with 1600 patients enrolled to-date (July 1, 2017).
Methods: Retrospective chart review and descriptive case series of all deceased patients enrolled in a MDR-TB treatment program in Ethiopia from February 2009 to December 2012 with at least 24 months of follow-up by December 2014. Cause of death was ascertained by clinicians caring for the enrolled patients.
Results: From February 2009 until December of 2012, 612 patients were initiated on second-line drugs and enrolled in MDR-TB treatment in two sites in Ethiopia and had ≥ 24 months of follow-up from a cohort with very high cure and completion (79.9%) (1). Among the initial 612 patients, 85 died (13.9%), median age of 30 (IQR 25-40), median number of prior TB treatments was 2 (IQR 2-3), and 27 (32%) were HIV co-infected. Median BMI among 54 patients was 14.85 (IQR 13.55-16.7) who had a recorded BMI. Median time to death was 4.4 months (IQR 1.5-11 months). The causes of death were TB-related in 45 (48.2%) (respiratory failure, massive hemoptysis, pneumothorax, *cor pulmonale* or complications of CNS TB); HIV-related in 7 (8.2%); related to adverse drug effects in 15 (17.6%) (renal failure, electrolyte wasting, neuropsychiatric effects and hepatotoxicity), or due to other causes in 22 (25.8%).
Conclusion: High rates of TB-related deaths were found among enrolled patients with ≥ 24 months of follow-up in an Ethiopian MDR-TB treatment program in a larger cohort with severe undernutrition, advanced disease and substantial HIV coinfection. Mortality was associated with profoundly low BMI and due to complications of long-term untreated TB such as respiratory failure, massive hemoptysis, pneumothorax, *cor pulmonale*. Our results argue for earlier diagnosis and access to appropriate MDR-TB treatment to diminish advanced lung disease and TB-related sequelae leading to mortality in Africa. Additional interventions targeting adverse drug effect management including nutritional supplementation should also be an essential component of MDR-TB treatment programs in resource-constrained settings.

[1] Meressa D, Hurtado RM, Andrews JR, Diro E, Abato K, Daniel T, Prasad P, Prasad R, Fekade B, Tedla Y, Yusuf H, Tadesse M, Tefera D, Ashenafi A, Desta G, Aderaye G, Olson K, Thim S, Goldfeld AE. Achieving high treatment success for multidrug-resistant TB in Africa: initiation and scale-up of MDR TB care in Ethiopia—an observational cohort study. *Thorax* 2015;70:1181-1188

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Umar Hussain, MHA, Performance Analysis and Improvement/Practice Improvement

An Alternative Pathway to Admission: The MGH/PHH Home Hospital Experience

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Introduction: As inpatient care constitutes a large percentage of total health care spending, avoiding hospitalization by delivering safe and effective care in alternative settings constitutes an important opportunity within population health. The traditional pathways for patients evaluated in the Emergency Department (ED) include discharge home, hospital observation or short-stay units, or admission to the hospital. To help increase inpatient capacity at Massachusetts General Hospital (MGH), we piloted a fourth option – admission to Home Hospital – from November-December of 2016. Our pilot aimed to include lower acuity patients requiring inpatient admission, but supported at home by an advanced home care team consisting of an MGH physician, Partners Healthcare at Home (PHH) Nurse Practitioner (NP), and PHH Registered Nurse (RN). Our goals for the pilot were to assess operational feasibility of Home Hospital at MGH, and to reduce hospital bed days for patients.

Methods: From October to December of 2016, we enrolled 11 patients in Home Hospital over a 4 week period. We limited the scope of the pilot to the following Ambulatory Care Sensitive Conditions: bacterial pneumonia, urinary tract infection, dehydration, chronic obstructive pulmonary disease (COPD), asthma, and chronic heart failure. On Monday through Friday from 8am-430pm, a physician in the ED monitored the admission dashboard for candidate patients, and evaluated candidates based on clinical inclusion and exclusion criteria. Non-clinical criteria for Home Hospital included patients that lived outside of a 5 mile radius from MGH. When a candidate patient was identified, the enrolling physician alerted the entire care team to initiate the process of transferring the patient from the ED (or Observation Unit) to the patient's home. The Home Hospital "admission" consisted of daily visits to the patient's home by the PHH NP, and twice daily visits by the PHH RN. The MGH Home Hospital physician visited the patient at home within 24 hours of admission, and reviewed patient updates and plans via phone with the PHH clinicians on non-visit days. During the pilot, 8 patients remained at home following their Home Hospital admission; 3 patients returned to MGH for clinical reasons.

Results: Based on the results and experience of the pilot, we resumed accepting patients into Home Hospital at MGH in April of 2017, with increased support and plans for scaling the initiative. To date, 33 patients have been enrolled into the program. A key feature of our re-launch is the new role of the Alternative Pathways Navigator (APN). The APN rounds daily with key individuals, and upon referral will discuss Home Hospital with the patient/family, and other members of the care team. Prior to discharge, the APN will facilitate the primary ED teams hand-off of patient to the care delivery team in the patients home.

Conclusion: The key lessons for dissemination are that intensive health care services can be delivered safely and effecitvely in a patients home. Moreover, patients and their families generally feel positive about receiving these services in their homes. The operational resources needed to deploy a home hospital scheme are significant, but can be aligned with other ED priorities to address capacity issues.

Home Hospital Referral Pathway

Patient with **potential admission** due to eligible condition **(CHF, COPD, CAP, UTI/Pyelo, Cellulitis)**

Clinical Condition Specific Criteria

Clinical judgment will help define the types of patients that will benefit from Home Hospital Services

Ambulatory Care Sensitive Conditions	**Exclusion Criteria:** Any of the below **disqualify** the patient for transfer to home care
Congestive Heart Failure	• New presentation of heart failure (no previous history of CHF • No response to IV diuretics in the ED or > 200 mg IV lasix per dose • ACS (Acute Coronary Syndrome) or cardiac ischemia • Acute respiratory failure with > 5L of O2 required for comfort • Unstable BP in the ED
COPD	• Altered mental status due to CO2 retention • Unresolving acidemia • Persistent need for BiPAP
Community Acquired Pneumonia	• Large pleural effusion on X-ray • Worse functional status since ED presentation • Acute respiratory failure with > 5L of O2 required for comfort • Active sepsis
Complicated UTI/pyelonephritis	• Large Pleural effusion on X-ray • Worse functional status since ED presentation • Acute respiratory failure with > 5L of O2 required for comfort • Active Sepsis
Cellulitis/Soft tissue infections	• Concern for pre-orbital cellulitis • Concern for drainable collection • Active sepsis

Clinical Stability

Any of the below **disqualify** the patient for transfer to home care if **no improvement during ED stay** (*with consideration of patient's baseline and other clinical factors*):

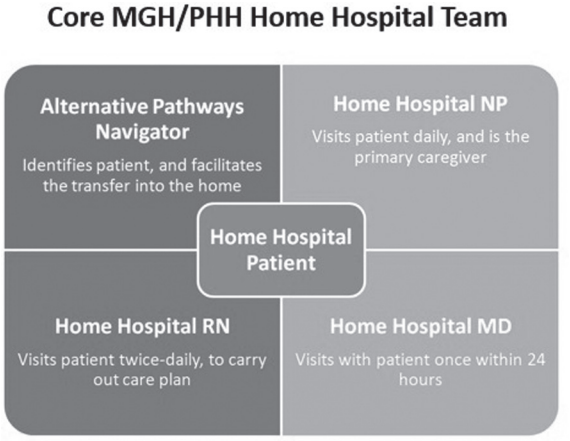
- **Vital sign abnormalities**: BP: Systolic <90, >200, HR: <50 bpm, >150 bpm, RR: >30 , Temp: <97 F, > 104 F
- **Laboratory**: FSBG <80 or >300; WBC count >30 K; new finding of Hgb <9; new finding of creatinine >2.5; elevated troponins (if checked)
- **Clinical status**: Inability to tolerate PO intake, pain not controlled on oral agents, concern for or symptoms of active cardiac ischemia, need for >5 L oxygen (unless on home oxygen), known history of arrhythmia, persistently altered mental status
- **Comorbidities**: Active malignancy, Unstable ESRD, Current immunosuppression

General Exclusion Criteria

Any of the below **disqualify** the patient for transfer to home hospital pathway

- Homelessness or inadequate living situation, home >5 miles from MGH hospital
- active substance abuse, uncontrolled psychiatric illness
- lack of social support; < 18 years of age

Home Hospital Referral Pathway



Core MGH/PHH Home Hospital Team

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William L. Hwang, MD, PhD, Radiation Oncology

Adjuvant versus early salvage post-prostatectomy radiotherapy for prostate cancer with adverse pathologic features: a multi-institutional analysis

W.L. Hwang[1], R.D. Tendulkar[2], A. Niemierko[1], S. Agrawal[12], K.L. Stephans[2], D.E. Spratt[3], J.W. Hearn[3], B.F. Koontz[4], W.R. Lee[4], J.M. Michalski[5], T.M. Pisansky[6], S.L. Liauw[7], M.C. Abramowitz[8], A. Pollack[8], D. Moghanaki[9], M.S. Anscher[10], R.B. Den[11], A.L. Zietman[1], A.J. Stephenson[2] and J.A. Efstathiou[1]

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Introduction: The use of radical prostatectomy (RP) as initial treatment of high-risk or locally-advanced prostate cancer has increased over the past two decades. However, patients with adverse pathologic features such as positive surgical margins, extraprostatic extension, and seminal vesicle invasion have a 40-70% risk of biochemical recurrence. These high-risk post-prostatectomy patients may be managed with adjuvant radiotherapy (ART) or surveillance followed by early salvage radiotherapy (ESRT) for biochemical recurrence. The purpose of this study is to evaluate freedom from biochemical failure (FFBF), freedom from distant metastases (FFDM), prostate-cancer specific survival (PCSS), and overall survival (OS) after ART vs. ESRT.

Methods: Individual data from 1566 patients who underwent post-prostatectomy ART or ESRT between 1987 and 2013 at 10 academic centers were pooled. Post-irradiation FFBF, FFDM, PCSS, and OS were compared using Kaplan-Meier and Cox regression methods. Propensity score (PS) matching was used to account for covariates potentially associated with treatment selection. All outcomes were measured from date of surgery to address lead-time bias.

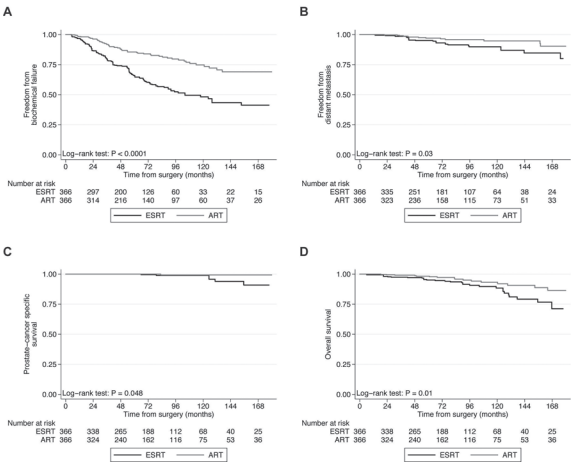
Results: In terms of baseline patient and treatment characteristics in the ART (n = 371; PSA <0.1 ng/mL) and ESRT (n = 1195; PSA 0.1-0.5 ng/mL) groups, the ESRT group had an earlier median year of surgery (2002 vs. 2006; P <0.001), lower pathologic T-stage (T3: 53% vs. 74%; P <0.001), lower Gleason score (Gleason 8-10: 20% vs. 29%; P <0.001), lower rate of positive margins (60% vs. 85%; P <0.001), less use of intensity-modulated RT (IMRT) (37% vs. 47%; P <0.001), and greater use of postoperative ADT (11% vs. 6%; P = 0.004). Median pre-ESRT PSA was 0.3 ng/mL (IQR, 0.2-0.4). Use of pelvic nodal RT was similar in the ESRT and ART groups (12% vs. 12%, P = 1.0). Post-RT BF occurred in 62 (17%) patients who received ART and 391 (33%) patients who received ESRT (P <0.0001). The crude rates of DM (4% vs. 7%; P = 0.034), prostate-cancer death (0.3% vs. 3.3%; P = 0.0005), and all-cause death (5% vs. 10%; P = 0.0049) were all lower in the ART cohort compared to the ESRT cohort. After PS-matching, median follow-up after surgery was 66 vs. 73 months for the ART and ESRT groups, respectively. ART was associated with significantly higher FFBF (12-yr: 69% vs. 43%; log-rank P <0.0001), FFDM (12-yr: 95% vs. 85%; log-rank P = 0.03), PCSS (12-yr: 99% vs. 94%; log-rank P = 0.048), and OS (12-yr: 91% vs. 79%; log-rank P = 0.01) (Figure). The number needed to treat with ART to prevent one recurrence was 4 and one death was 9 at twelve years. ART, lower Gleason score, lack of seminal vesicle invasion, nodal irradiation, and postoperative androgen deprivation therapy (ADT) were favorable prognostic features on multivariate analysis for BF (Table). To account for the unknown subset of patients in the ART group that would never have recurred after surgery, we performed a sensitivity analysis that determined the decreased risk of BF associated with ART only lost statistical significance when more than 56% of ART patients were assumed to have been cured by surgery alone. This threshold is greater than the expected 10- and 15-year FFBF of 46% and 38%, respectively, after radical prostatectomy alone as determined by the contemporary, dynamic post-prostatectomy MSKCC nomogram, indicating that the difference in FFBF cannot be attributed to successful surgery alone.

Conclusion: To the best of our knowledge, this represents the largest multi-institutional study to date comparing ART to ESRT. Adjuvant RT was associated with reduced biochemical recurrence, distant metastases, and death compared to early salvage RT for high-risk prostate cancer patients. The current use of ART in high-risk patients is less than 10%. Pending prospective validation, our findings suggest that a greater proportion of such men may benefit from adjuvant RT, especially those for whom the estimated risk of post-prostatectomy recurrence is greater than 50%.

Multivariate Cox regression analyses of factors predicting biochemical failure after radical prostatectomy and post-operative radiotherapy in patients with pT2N0M0/R1 or pT3N0M0/R0-1 prostate adenocarcinoma.

	Before PS matching		After PS matching	
	HR (95% CI)	P	HR (95% CI)	P
ART vs. ESRT	0.42 (0.31-0.56)	<0.0005	0.32 (0.23-0.45)	<0.0005
Age at surgery	0.99 (0.98-1.01)	0.36	1.00 (0.98-1.02)	0.85
Year of surgery	1.03 (1.01-1.05)	0.004	1.02 (0.99-1.05)	0.20
Pathologic T-stage	----------	----------	----------	-------
T2	Reference	----------	Reference	-------
T3a	1.33 (1.06-1.66)	0.01	1.18 (0.80-1.74)	0.41
T3b	2.30 (1.77-2.98)	<0.0005	1.92 (1.25-2.95)	0.003
Surgical Gleason score	1.66 (1.49-1.86)	<0.0005	2.06 (1.75-2.42)	<0.0005
Surgical margin (-/+)	0.76 (0.63-0.92)	0.004	1.33 (0.87-2.04)	0.19
Omitting nodal RT	2.01 (1.40-2.88)	<0.0005	2.24 (1.35-3.73)	0.002
RT dose (Gy), prostate fossa	0.96 (0.93-1.00)	0.03	0.96 (0.91-1.00)	0.06
Postoperative ADT	0.55 (0.39-0.78)	0.001	0.30 (0.13-0.68)	0.004

ADT, androgen deprivation therapy; ART, adjuvant radiation therapy; ESRT, early-salvage radiation therapy; PS, propensity score; RT, radiation therapy.



Kaplan-Meier curves of (a) freedom from biochemical failure, (b) freedom from distant metastases, (c) prostate cancer-specific survival, and (d) overall survival after ART versus EBRT in a propensity score-matched cohort of patients with pT2N0M0/R1 or pT3N0M0/R0-1 prostate adenocarcinoma.

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William L. Hwang, MD, PhD, Radiation Oncology

Clinical outcomes of metastatic lung cancer patients treated with PD-1/PD-L1 inhibitors and thoracic radiotherapy

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Introduction: Immune checkpoint inhibitors (CPIs) have become integral in the treatment of advanced lung cancer but are associated with unique immune-related adverse events (IRAEs). Many of these patients will also receive thoracic radiotherapy (TRT). A better understanding of potential toxicities when combining CPIs with TRT is imperative.
Methods: We performed a retrospective cohort study (2013-2016) of metastatic lung cancer patients treated with PD-1/PD-L1 inhibitors at a U.S. academic medical center. Primary outcomes were IRAEs including pneumonitis (NCI-CTCAE v4.0) and survival measured from time of CPI initiation.
Results: Among 164 patients (95% non-small cell, 5% small cell), median overall survival (OS) was 12.1 months. Baseline characteristics (Table 1) were similar in patients who received TRT (n = 73) and those who did not (n = 91) except fewer patients who received TRT had adenocarcinoma (49% vs. 75%, p = 0.0011) and targetable mutations (*EGFR/ALK/ROS1*; 4% vs. 16%, p = 0.012). Rates of grade ≥2 IRAEs (13.7% vs. 15.4%, p = 0.83), all-grade pneumonitis (8.2 vs. 5.5%, p = 0.54), and grade ≥2 pneumonitis (4.1 vs. 3.3%, p = 1) were not significantly different between the +TRT and -TRT cohorts. Median TRT dose was similar between those patients who developed pneumonitis and those who did not (52.8 vs. 50.4 Gy). Most patients (78%) were treated with TRT a median of 8.6 months (range: 0.1-69 months) before CPI initiation. None of the 16 patients who received TRT between CPI cycles (median 44 Gy), TRT after CPI (median 22 Gy), or more than one course of TRT developed symptomatic pneumonitis. Multivariate analysis (Table 2) demonstrated all-cause mortality was significantly lower in patients with grade ≥2 IRAEs (HR 0.45, 95% CI: 0.22-0.93; p = 0.031) or treated with fewer chemotherapy lines (HR 1.21, 95% CI: 1.05-1.40; p = 0.009). Furthermore, receipt of TRT showed a trend towards reduced all-cause mortality (HR 0.66, 95% CI: 0.42-1.01; p = 0.057).
Conclusion: Patients responding to CPIs generally receive more treatment and therefore may be more prone to develop toxicities with higher cumulative doses. Alternatively, it may be that augmentation of the anti-tumor immune response by CPIs cannot be decoupled from an anti-self immune response resulting in IRAEs akin to the challenges in separating graft versus leukemia (GVL) and graft versus host disease (GVHD) after allogeneic hematopoietic stem cell transplantation. While development of grade ≥2 IRAEs was associated with improved survival overall, a small subset of patients developed severe and even rapidly fatal toxicities. The association between more chemotherapy lines and reduced survival may be secondary to more advanced or treatment-refractory disease at the time of CPI initiation or the immunosuppressive properties of many chemotherapeutic agents. The trend towards increased OS with TRT despite significantly fewer patients in the +TRT group harboring targetable mutations is intriguing. It has been postulated that a lack of antigenic mutations and other mechanisms of immune evasion may underlie resistance to CPIs. In certain situations, RT can potentiate the efficacy of immunotherapy,

even re-stimulating a durable systemic response in disease that has become refractory to CPIs alone. A recent small single-institution secondary analysis of KEYNOTE-001 found that patients who received any radiotherapy prior to pembrolizumab had significantly longer PFS and OS. While the few patients who received TRT (n = 24) at a median of 11.5 months before pembrolizumab had a higher incidence of low-grade pulmonary toxicity, there was no difference in grade ≥3 pneumonitis, consistent with our findings. Pending prospective validation, our results suggest that definitive TRT before CPI and palliative TRT between CPI cycles or after CPI completion does not increase the risk of symptomatic IRAEs including pneumonitis compared to CPIs alone.

Table 1. Baseline characteristics of the study population.

Characteristic	Overall (n = 164)	+TRT (n = 73)	-TRT (n = 91)	p-value
Age at diagnosis (median, range)	64 (34-84)	65 (39-84)	63 (34-83)	0.79
Gender (% male)	57	58	56	0.88
Smoking history (%)	87	88	87	1
COPD (%)	62	68	57	0.15
Supplemental oxygen (%)	11	12	10	0.63
Histology (% adenocarcinoma)	63	49	75	0.0011
Targetable mutation: EGFR, ALK, ROS1 (%)	11	4	16	0.012
Prior chemotherapy (%)	96	97	95	0.46
Chemotherapy lines (median, range)	1 (0-8)	1 (0-8)	1 (0-7)	0.48
Prior non-lung cancer RT (%)	7	11	4	0.14
PD-1 inhibitor (%)*	94	95	93	1
CPI cycles (median, range)	4 (1-55)	5 (1-55)	3 (1-36)	0.17
Baseline LDH (IU/L)**	228	211	242	0.23

COPD, chronic obstructive pulmonary disease; LDH, lactate dehydrogenase; RT, radiotherapy

* All patients in this study received PD-1 inhibitors and/or PD-L1 inhibitors.

** Baseline LDH (normal range 98-192 IU/L) before CPI initiation was available for 84 of 164 patients.

Table 2. Univariate and multivariate Cox regression analyses of all-cause mortality.

	Univariate		Multivariate	
Variable	HR (95% CI)	p-value	HR (95% CI)	p-value
Age at diagnosis (yr)*	1.01 (0.99-1.04)	0.24		
Gender (F = 0, M = 1)**	1.16 (0.76-1.78)	0.48	1.21 (0.79-1.87)	0.39
Smoking**	0.69 (0.39-1.23)	0.21	0.82 (0.44-1.52)	0.53
Smoking pack-years*	1.00 (0.99-1.01)	0.54		
COPD**	0.75 (0.49-1.13)	0.17		
Supplemental oxygen**	1.51 (0.83-2.76)	0.18		
Targetable mutation**	1.41 (0.78-2.55)	0.26		
Chemotherapy**	0.90 (0.36-2.26)	0.82		
Chemotherapy lines*	1.13 (1.00-1.27)	0.049	1.21 (1.05-1.40)	0.009
Prior non-lung cancer RT**	0.59 (0.24-1.46)	0.25		
Thoracic RT**	0.69 (0.45-1.07)	0.095	0.66 (0.42-1.01)	0.057
Thoracic RT dose (Gy)*	0.99 (0.96-1.01)	0.25		
Any RT**	0.81 (0.52-1.28)	0.37		
Baseline LDH (elevated vs. normal)**	1.23 (0.72-2.11)	0.45	0.88 (0.53-1.45)	0.61
Grade ≥2 IRAE**	0.55 (0.28-1.07)	0.08	0.45 (0.22-0.93)	0.031

COPD, chronic obstructive pulmonary disease; Gy, Gray; LDH, lactate dehydrogenase; RT, radiotherapy

* Continuous variable

** Binary variable

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Gi Hye Im, Orthopedics

Fungal Spinal Epidural Abscess: Characteristics of FSEA and the Differences between FSEA and BSEA

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Introduction: Fungal spinal epidural abscess (FSEA) is a rare entity, with few reports that describe its clinical features, diagnosis, treatment, and outcomes. Similarly, the characteristics of FSEA and the more common bacterial spinal epidural abscess (BSEA) have not been compared. Therefore, we describe the clinical features, diagnosis, treatment, and outcomes of FSEA and report differences from bacterial spinal epidural abscess (BSEA).

Methods: We reviewed the electronic medical records of patients with FSEA who were treated within our hospital system in the last 23 years. We compared our findings to all reported FSEA cases in the English-language literature from 1952 to 2017. We compared our FSEA cases to the BSEA cases in our database.

Results: From a spinal epidural abscess database of 879 patients, we identified nine patients with FSEA. *Aspergillus fumigatus* was isolated from 2 (22%) patients, and *Candida* species were isolated from 7 (78%). Local spine pain, neurologic deficit, and fever were demonstrated in 89%, 50%, and 44% of FSEA cases, respectively. Patients with FSEA had longer symptom duration (>2 weeks) prior to presentation than those with BSEA (p=0.020). Fifty-six percent of FSEAs involved the thoracic spine, and 89% were located anterior to the thecal sac. Fifty-nine patients with FSEA were identified through literature review. *Aspergillus* and *Candida* were responsible for 60% and 29% of cases, respectively. FSEA was less likely to cause fungemia than BSEA was to cause bacteremia (p=0.023). Additionally, FSEA cases had a higher probability of having concurrent immunosuppression, vertebral osteomyelitis, and a history of malignant tumor than BSEA cases (p=0.029, p=0.040, and p=0.044, respectively). Finally, the rate of recurrence and mortality in FSEA are higher than in BSEA.

Conclusion: The most common pathogens identified in FSEA are *Aspergillus* and *Candida* species. Empiric treatment for FSEA should cover these species while definitive identification is pending. The three most common symptoms for FSEA are local spine pain, neurologic deficit, and fever. The thoracic and lumbar regions of the spine are most likely to be involved. FSEA has a higher rate of recurrence and mortality than BSEA.

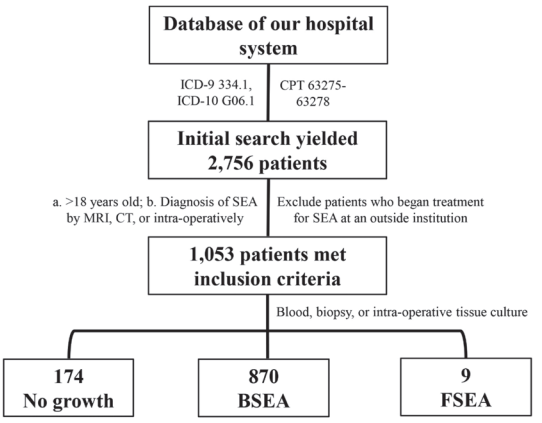

Figure 1. Patient inclusion/exclusion flow chart. ICD = International Classification of Diseases; CPT = Current Procedural Terminology; SEA = Spinal Epidural Abscess; MRI = Magnetic Resonance Imaging; CT = Computed Tomography; BSEA = Bacterial Spinal Epidural Abscess; FSEA = Fungal Spinal Epidural Abscess.

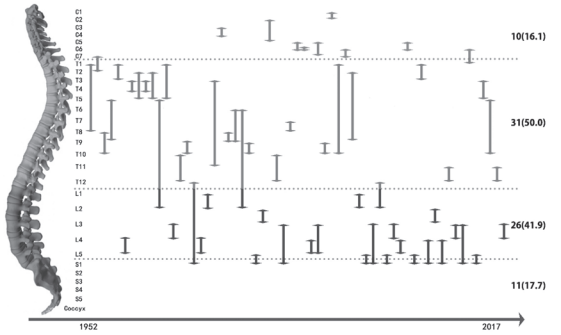

Figure 2. Distribution of fungal spinal epidural abscesses. The bars indicate the vertebral levels involved in the fungal spinal epidural abscess. The colors of the bars correspond to the different regions of the spine (cervical = orange, thoracic = green, lumbar = blue, sacral = purple). The numbers to the right of the figure indicate counts and the corresponding percentage of patients with fungal spinal epidural abscesses involving that region of the spine.

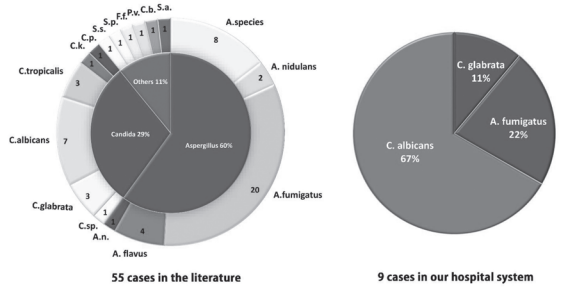

Figure 3. Pathogens of fungal spinal epidural abscesses. A = *Aspergillus*; C = *Candida*; A.n. = *Aspergillus niger*; C.p. = *Candida parapsilosis*; C.k. = *Candida Kefyr*; C.sp. = other *Candida* species; S.s. = *Sporotrichum sckenkii*; S.p. = *Scedosporium prolificans*; F.f. = *Fusarium falciforme*; P.v. = *Phaeoacremonium venezuelense*; C.b. = *Cunninghamella bertholletiae*; S.a. = *Scedosporium apiospermum*.

Table 3. Comparison of fungal spinal epidural abscess and bacterial spinal epidural abscess.

Variables	FSEA n=9	BSEA n=870	p-value
Demographics			
Age (years)	54 (48-68)	59 (48-69)	0.703
Male	67 (6)	61 (533)	>0.999
BMI (kg/m^2)[a]	21.4 (17.6-25.1)	27.5 (23.9-32.7)	0.110
Habits			
Smoking	44 (4)	47 (412)	>0.999
Alcohol use	11 (1)	17 (151)	>0.999
Intravenous drug use	22 (2)	19 (162)	0.678
Medical comorbidities			
Low bone density	44 (4)	17 (146)	0.051
Spinal osteoarthritis	33 (3)	32 (277)	>0.999
Diabetes mellitus	22 (2)	23 (203)	>0.999
Active malignancy	0	7.6 (66)	>0.999
Hemodialysis	0	4.4 (38)	>0.999
Immunocompromised	44 (4)	14 (123)	**0.029**
Recent spinal trauma	11 (1)	9.8 (85)	0.606
Prior surgery within 5 years[b]	0	19 (166)	0.221
History of malignancy	44 (4)	16 (139)	**0.044**
Lab test			
White blood cell count (1000/mm^3)	12.6 (9.5-13.9)	12.1 (8.7-16.6)	0.960
Erythrocyte sedimentation rate (mm/hr)[a]	81 (45-110)	88 (62-107)	0.497
C-reactive protein level (mg/L)[a]	88 (71-136)	130 (42-204)	0.656
Presentation characteristics			
Neurological status			
Motor deficit[a]	50 (4)	37 (312)	0.479
Sensory deficit	0	19 (165)	0.222
Radicular pain	33 (3)	28 (245)	0.717
Urinary/fecal incontinence/retention	11 (1)	14 (119)	>0.999
Other symptoms			
Local spine pain	89 (8)	97 (841)	0.269
Fever[c]	44 (4)	29 (248)	0.287
Fungemia/bacteremia	33 (3)	71 (615)	**0.023**
Symptom duration prior to presentation >2 weeks[a]	67 (6)	28 (247)	**0.020**
Vertebral osteomyelitis	89 (8)	54 (468)	**0.044**
Paraspinal abscess			
Psoas abscess	22 (2)	17 (150)	0.658
Prevertebral/retropharyngeal abscess	0	8.2 (71)	>0.999
Other paraspinal abscess	22 (2)	33 (284)	0.726
Abscess characteristics			
Region of spine			
Cervical	0	12 (107)	<0.485
Cervicothoracic	11 (1)	5.8 (50)	
Thoracic	44 (4)	22 (191)	
Thoracolumbar	0	6.9 (60)	
Lumbar/sacral	44 (4)	46 (398)	
Multifocal/>2 contiguous regions	0	7.4 (64)	
Location of abscess relative to thecal sac[a]			
Anterior	89 (8)	54 (471)	0.186
Posterior	0	26 (225)	
Circumferential	0	7.6 (66)	
Multiple locations	11 (1)	12 (103)	
Number of involved vertebrae	2 (2-3)	3 (2-5)	0.283
Treatment			
Surgery	67 (6)	64 (557)	>0.999
Instrumentation	11 (1)	20 (177)	0.695
Outcomes			
Residual motor deficit[a]	17 (1)	20 (160)	>0.999
Recurrence	22 (2)	3.3 (27)	**0.037**
Mortality	44 (4)	12 (107)	**0.018**
Follow-up (weeks)	11 (2-47)	22 (5-90)	0.446

Bold indicates statistical significance (p-value < 0.05).
Nonparametric continuous variables are presented with median and interquartile range. Categorical variables are presented with frequencies and numbers.
FSEA = Fungal Spinal Epidural Abscess; BSEA = Bacterial Spinal Epidural Abscess; BMI = Body Mass Index.
[a] *BMI was available in 2 cases (2%) with FSEA and 339 cases (39%) with BSEA; Erythrocyte sedimentation rate was available in 7 cases (78%) with FSEA and 629 cases (72%) with BSEA; C-reactive protein level was available in 4 cases (44%) with FSEA and 452 cases (52%) with BSEA; Motor deficit was available in 8 cases (89%) with FSEA and 842 cases (97%) with BSEA; Symptom duration prior to presentation was available in 868 cases (100%) with BSEA; Location of abscess relative to thecal sac was available in 865 cases (99%) with BSEA; Residual motor deficit was available in 6 cases (67%) with FSEA and 792 cases (91%) with BSEA.*
[b] *prior surgery = previous surgery at the site of the SEA.*
[c] *More than 100.4°F*

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Gi Hye Im, Orthopedics

A Classification Scheme for Epidural Spinal Cord Compression in Spinal Epidural Abscess

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Introduction: Magnetic resonance imaging (MRI) has been the most common method to diagnose spinal epidural abscess (SEA) and evaluate the degree of epidural spinal cord compression (ESCC). High-grade ESCC frequently serves as an indication for surgical decompression, while no consensus exists in the literature about the precise definition of this term in SEA. The advancement of treatment paradigms in patients with SEA requires a clear grading scheme of ESCC, as the degree of ESCC often serves as a major determinant in the decision to operate. The purpose of this study was to develop a classification scheme for ESCC in patients with SEA and to determine whether this scoring scheme is associated with neurologic deficit at admission, treatment, and outcomes.

Methods: We conducted a retrospective cohort study using electronic records in our hospital system. All patients were over 18 years old and had a clinically and radiologically documented cervical or thoracic SEA during the period 1995-2016. All patients had both sagittal and axial T2-weighted MR images prior to initiation of treatment. We developed a 5-point classification scheme of ESCC. Grade 1: epidural impingement, no deformation of thecal sac; grade 2: deformation of thecal sac, without cord abutment; grade 3: deformation of thecal sac, with cord abutment, without cord compression; grade 4: spinal cord compression, with CSF visible around cord; grade 5: spinal cord compression, no CSF visible. We analyzed association of ESCC grade with patients' neurologic deficit at admission, treatment, and outcomes through univariate logistic regression.

Results: The study included 351 patients with SEA. The most common degree of ESCC was grade 5 (39%), followed by grade 4 (26%), grade 3 (17%), grade 2 (15%), and grade 1 (3%). Compared to grades 1 and 2, patients with grade 5 compression were more likely to exhibit pre-treatment motor deficit ($p<0.001$), sensory change ($p<0.001$), and bladder or bowel dysfunction ($p=0.030$). Similarly, patients with grade 4 compression were more likely to have motor weakness at presentation ($p=0.017$). The presence of grade 5 compression was associated with an increased likelihood of undergoing surgical management ($p<0.001$) as well as with presence of a residual motor deficit at follow-up ($p=0.002$). Our scheme was not associated with recurrence or mortality.

Conclusion: With a cohort of 351 patients, we provided a framework to describe the grade of spinal cord compression in SEA. High-grade ESCC was most common in our study as a result of the narrow spinal canal of the cervical and thoracic spine. More compression was associated with worse neurologic status due to severe myelopathy and spinal cord dysfunction. High-grade ESCC was associated with poor outcome of residual motor deficit at last follow-up, resulting from higher likelihood of pre-treatment weakness. The grade of ESCC was not associated with other poor outcomes, e.g. mortality, recurrence.

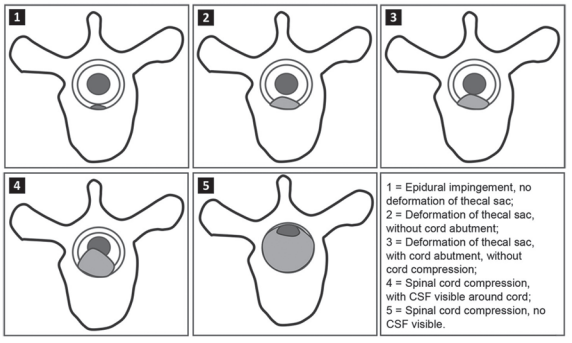

Figure 1. Schematic representation of the 5-point epidural spinal cord compression grading scale.

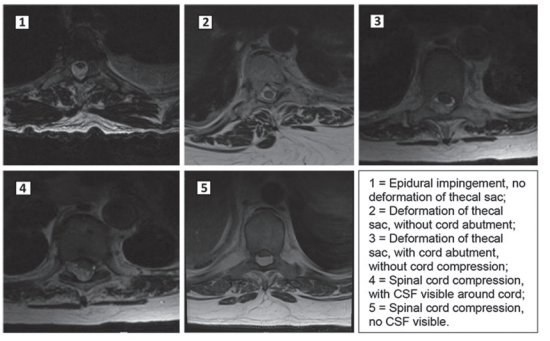

Figure 2. Axial T2-weighted MR images representing progressive grades of epidural spinal cord compression.

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Rabab Z. Jafri, M.D., Medicine - Endocrine-Diabetes

Automated Glucagon Administration for the Treatment of Post-bariatric Hypoglycemia

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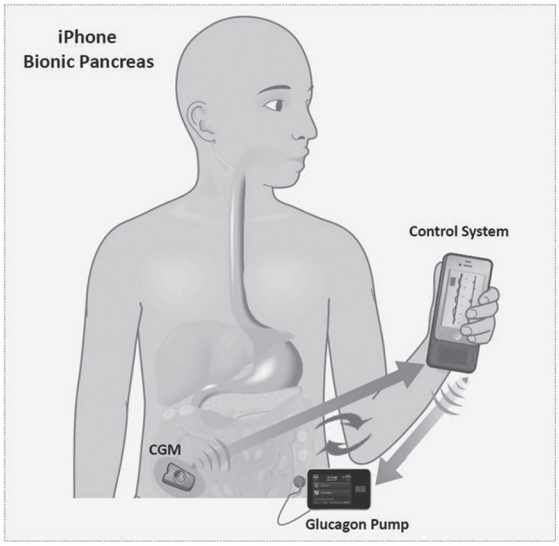
Introduction: A rare complication of bariatric surgery, especially of the Roux-en-Y gastric bypass (RYGB), is development of post-bariatric hypoglycemia (PBH). The frequency of severe hypoglycemia in patients with RYGB is low (0.2%) but mild hypoglycemia occurs much more frequently (up to a third of post-surgical cases) and can be challenging to control. Treatment of hypoglycemia often leads to spikes in blood sugar which triggers more hypoglycemia. Hypoglycemia unawareness can develop and lead to complications such as loss of consciousness and seizures. An emergency glucagon injection is currently the standard treatment for severe hypoglycemia, but we propose that automated administration of microdose glucagon via a closed-loop bionic pancreas system will be effective at reducing the incidence and severity of hypoglycemia in patients with PBH.

Methods: This was a 2 week randomized, placebo-controlled study. 10 participants with post-bariatric hypoglycemia who reported continued hypoglycemia despite their current medication regimen (including acarbose and/or octreotide) were included. During the study, participants managed their hypoglycemia in a usual care fashion while, in addition, receiving either glucagon or placebo each day through a closed-loop glucagon-only bionic pancreas system.

Results: There was a statistically significant reduction in percentage of time spent with BG <70mg/dl (3.07% ± 3.86 vs 5.87% + 5.76 p = 0.009). A nominal reduction in percentage of time <60mg/dl (1.26% ± 2.04 vs 2.31% ± 2.49 p = 0.06) on glucagon vs. placebo days was seen. There was no difference in mean glucose levels (112 ±10 mg/dl vs 110 ± 11 mg/dl, p = 0.07). Mean total daily glucagon dose was 8.34 ± 3.76 mcg/kg/day. Subjects were able to correctly guess their assignment to glucagon or placebo 23% of the time. Nausea severity on visual analogue scale was low and did not differ significantly between glucagon versus placebo (0.4 ± 0.5 vs 0.4 ± 0.7, p=0.52)

Conclusion: In patients with post-bariatric hypoglycemia with persistent hypoglcemia despite typical therapy, automated glucagon administration significantly reduced hypoglycemia without increased mean glucose or hyperglycemia. These findings suggest that automated delivery of microdose glucagon is a safe and efficacious way to reduce hypoglycemia in patients with post-bariatric hypoglycemia.



Glycemic Control and Glucagon Usage

	Glucagon Mean ± SD	Placebo Mean ± SD	P value
% CGM 70–180 mg/dl	92.7 ±7.0	89.3 ± 8.2	0.01
% CGM <70 mg/dl	3.1 ± 3.8	5.9 ± 5.7	0.01
Glucagon TDD (mcg/kg/day)	8.3 ± 3.8		
Nausea severity (Visual Analogue Scale)	0.4 ± 0.5	0.4 ± 0.7	0.52

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Rafaella J. Jakubovic, B.S., Psychiatry

Dissemination of Evidence-Based Treatments for PTSD among Community Providers: Impact of Additional Refresher Training

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Introduction: As many as 40% of post-9/11 veterans seek care outside of the VA. Despite growing proportions of post-9/11 veterans and their families seeking care in community settings, reports suggest few community providers are trained in or utilizing evidence-based treatments (EBTs) for PTSD in practice, and that there is both a desire and need in community settings for additional training and supervision to enhance capacity for high quality care for military-related mental health concerns. In addition, reports suggest that training alone may not be sufficient for clinicians to retain information provided, leading to low preparedness to utilize the protocol once appropriate patients are identified. We held four 2-day trainings in one of two EBTs for PTSD: Cognitive Processing Therapy (CPT) and Prolonged Exposure Therapy (PE). A subset of participants then received 6 months of weekly consultation. However, follow up surveys from the initial trainings revealed that over half of participants reported a lack of comfort with the protocol six months later. As a result, we conducted two one-day Refresher Trainings held 12 to 17 months following the initial protocol-specific trainings. We then assessed for provider preparedness, knowledge of, and comfort with the EBT protocol at pre- and post-Refresher Training, as well as implementation of the protocol at 3 months post-Refresher Training, including with military-connected populations.

Methods: We held two 2-day PE trainings and two 2-day CPT trainings (N = 44-47 at each training). A subset of participants (n = 8-10 per group) from each training participated in 6 months of weekly group phone consultation. Pre- and post-training survey results from the initial trainings indicate that the trainings and consultations were successful; participants reported increased knowledge of the EBT as well as comfort and preparedness to utilize the protocols. However, at 6-month follow up from the initial trainings, 58% (N = 134) of participants reported that they were not at all or moderately comfortable with the protocol. All participants from each of the four 2-day trainings were then invited to attend one of two full-day Refresher Trainings held 12-17 months after their initial training. The Refresher Trainings included presentation on broad topics of participant-reported interest session (e.g. PTSD assessment, client/therapist avoidance, military culture) in a combined morning session, and higher-level protocol-specific topics in afternoon break-out sessions (e.g. identifying stuck points for CPT, imaginal exposure for PE). Refresher Training participants were assessed at pre-training, post-training, and 3 months post-training.

Results: Thus far, we have collected pre-training and post-training data from participants of both Refresher Trainings (N = 40) as well as 3-month follow up data from the first training (N = 18). McNemar's χ^2 tests reveal a significant increase from pre-training to post-training in participants who report feeling mostly or fully prepared to treat service members and veterans (52.5% vs. 80.0%), χ^2 (1, N = 40) = 9.31, p = .002, and military-connected family (67.5% vs. 85.0%), χ^2 (1, N = 40) = 5.44, p = .02, confident to address military culture (50.0% vs. 70.0%), χ^2 (1, N = 40) = 6.40, p = .01, confident to use the EBT (56.4% vs. 66.7%), χ^2 (1, N = 40) = 4.00, p < .05, and knowledgeable about the protocol (50.0% vs. 84.6%), χ^2 (1, N = 40) = 14.00, p < .001. Additionally, there is a significant increase from pre-training to post-training in PE participants who report feeling mostly or fully confident to create a hierarchy (60.0% vs. 100.0%), χ^2 (1, N = 20) = 8.00, p = .005, and do in vivo exposure (60.0% vs. 100.0%), χ^2 (1, N = 20) = 8.00, p = .005, and a significant increase from pre-training to post-training in CPT participants who report feeling mostly or fully confident to identify stuck points (55.0% vs. 80.0%), χ^2 (1, N = 20) = 5.00, p = .03, and use Socratic questioning (35.0% vs. 65.0%), χ^2 (1, N = 20) = 6.00, p = .01. Change from pre-training to post-training on these variables was not significantly different for participants who received consultation, with the exception of PE trainees who had not received consultation reporting significantly greater improvement in confidence to create a hierarchy and do in vivo exposure (M = 0.62, SD = 0.51) than those who received consultation (M = 0.0, SD = 0.0), t(17) = 2.93, p < .01. At post-training, 84.6% reported that the Refresher Training was an extremely valuable addition to the initial training (N = 39).

Conclusion: These findings suggest that the addition of a Refresher Training may be a valuable enhancement for community providers utilizing EBTs for PTSD who have received an initial training. Specifically, the Refresher Training may increase knowledge of and comfort with the protocol, preparedness to treat service members and military families, and implementation of EBTs in practice, regardless of whether the participant received consultation. Three-month follow up data will also be presented for both Refresher Trainings.

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Aisha James, MD MEd, Medicine

Impact of a Population Health Management Intervention on Racial Health Disparities in Cardiovascular Disease

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Introduction: Healthcare systems are using population health management (PHM) programs to improve the quality of cardiovascular disease care. Whether these programs also improve racial/ethnic disparities in care is unclear.
Methods: Eighteen primary care practices were studied from 7/1/14-12/31/14. All used the same PHM information technology system (TopCare, SRG Technology) to identify and track patients with cardiovascular disease or hypertension. To help patients meet quality metrics, 8 intervention practices were assigned a dedicated central population health coordinator and 10 control practices used office-based staff. Outcomes included clinically relevant low-density lipoprotein (LDL) cholesterol and/or blood pressure (BP) measures. The LDL goal was LDL < 100 mg/dL, or prescription of a high dose "statin". The BP goal was < 140/90 mm Hg for patients < 60 years, < 150/90 mm Hg for patients ≥ 60 years, or prescription of ≥3 BP lowering medications. We examined changes in meeting LDL and BP goals in intervention and non-intervention practices by self-reported race/ethnicity (non-Hispanic white, non-Hispanic Black, or Hispanic). Analyses used logistic regression with generalized estimating equations for repeated measures, adjusted for age, gender, health insurance, primary language, patient-provider attribution, and whether care was received in a health center.
Results: There were 12,555 participants in the LDL analyses (85.5% non-Hispanic white, 4.8% non-Hispanic black, 4.7% Hispanic), and 41,183 participants in the BP analyses (79.7% non-Hispanic white, 7.5% non-Hispanic black, 6.6% Hispanic). Across all practices at baseline, there were racial/ethnic disparities (LDL: non-Hispanic white 70.3% at goal, non-Hispanic black 64.2%, Hispanic 68.5%, p=.007; BP: non-Hispanic white 76.4% at goal, non-Hispanic black 73.4%, Hispanic 74.8%, p=.0003). Comparing intervention and non-intervention practices before and after the study period, non-Hispanic white patients in intervention practices had significantly increased odds of LDL control (OR 1.20 95% CI 1.09 – 1.32), while Non-Hispanic black (OR 1.15 95%CI 0.80 – 1.65) and Hispanic (OR 1.29 95% CI 0.66 – 2.53) patients saw similar, but not statistically significant, changes. For odds of BP control, non-Hispanic white patients in intervention practices saw improvement (OR 1.13 95% CI 1.05 – 1.22), which was similar, though not significant, for non-Hispanic black patients (OR 1.17 95% CI 0.94 – 1.45), but Hispanic (OR 0.90 95% CI 0.59 – 1.36) patients did not. Interaction testing confirmed that pre-existing disparities did not improve (p=0.73 for LDL and p=0.69 for BP).
Conclusion: The intervention improved the odds of cardiovascular risk factor control in most analyses, though with wide confidence intervals in racial/ethnic minority patients, likely related to smaller sample sizes. However, there were no large changes in disparities. Future population health management interventions should explicitly target both healthcare equity and quality.

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Ex Vivo Profiling of PD-1 Blockade Using Organotypic Tumor Spheroids

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Introduction: Despite the unprecedented success of PD-1/PD-L1 immune checkpoint blockade (ICB) in several cancers, resistance remains a challenge for the majority of patients, and robust biomarkers to guide treatment are lacking. Development of more sophisticated tissue culture models that incorporate features of the tumor immune microenvironment may help to overcome these barriers and facilitate identification of therapies to combat anti-PD-1/PD-L1 resistance. Here, we report a novel approach for evaluating *ex vivo* response to ICB using murine- and patient-derived organotypic tumor spheroids (MDOTS/PDOTS) cultured in a 3-dimensional microfluidic system.
Methods: To overcome these challenges and model ICB *ex vivo* we adapted a 3D microfluidic device to the short-term culture of murine- and patient-derived organotypic tumor spheroids (MDOTS/PDOTS). Following limited collagenase digestion of fresh tumor specimens, multicellular organotypic spheroids with autologous immune cells were isolated. MDOTS/PDOTS were analyzed by flow cytometry or loaded in collagen into the central channel of the device for exposure to anti-PD-1 or anti-CTLA-4 antibodies.

Results: We demonstrate that spheroids isolated from fresh mouse and human tumor samples retain autologous lymphoid and myeloid cell populations, including antigen-experienced tumor infiltrating CD4 and CD8 T lymphocytes, and respond to ICB in short-term *ex vivo* culture. Tumor killing was recapitulated *ex vivo* using MDOTS derived from the anti-PD-1 sensitive MC38 syngeneic mouse cancer model, whereas relative resistance to anti-PD-1 therapy was preserved in the CT26 and B16F10 syngeneic models. Systematic cytokine/chemokine profiling following PD-1 blockade in PDOTS from patients with melanoma and other tumors identified significant induction of the immunoattractants CCL19 and CXCL13, which was confirmed *in vivo* and correlated with evidence of intratumoral immune cell infiltration. Resistance to anti-PD1 treatment in MDOTS and PDOTS also tracked with co-induction of immune suppressive chemokines. *Ex vivo* profiling revealed TBK1/IKKe inhibition as a novel therapeutic strategy to enhance sensitivity to PD-1 blockade in this setting, which effectively predicted tumor response *in vivo*.
Conclusion: Here we describe a novel approach for functional evaluation of ICB using organotypic tumor spheroids in a three-dimensional microfluidic culture system. These findings demonstrate feasibility of *ex vivo* profiling of PD-1 blockade, and offer a novel functional approach to facilitate precision immuno-oncology and develop novel therapeutic combinations. The ability to measure *ex vivo* PD-1 responses in MDOTS from well-studied syngeneic murine tumors and identify novel immunotherapy combinations provides a distinct advantage over organoids, which lose the native TME. Larger prospective studies are needed to assess prediction of clinical benefit by PDOTS cytokine profiling or *ex vivo* killing. Regardless, we validate the ability of short-term organotypic tumor spheroid culture to identify effectors of PD-1 blockade and specific interventions that can counteract resistance, a much needed advance given the challenges of testing the massive number of potential combination therapies *in vivo*. This system thus represents a functional precision medicine approach to drive clinical-translational efforts to develop novel combinations and ultimately personalized immunotherapy.

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Yisi D. Ji, BS, Oral and Maxillofacial Surgery

What Is Important for Confirming Negative Margins When Resecting Mandibular Ameloblastomas?

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Introduction: The ameloblastoma is a benign aggressive neoplasm usually treated by segmental or marginal resection. Ameloblastomas infrequently recur (3.6 to 13%) if managed with resection with adequate margins (≥1 cm), whereas recurrence rates up to 93% have been reported with enucleation and curettage. Frozen sections are commonly used for malignant lesions (eg, squamous cell carcinoma), with reported accuracy rates of 98.3% compared with the same section fixed in formalin and embedded in paraffin. However, the utility of frozen sections, often curetted from cancellous bone at bony resection margins, to detect benign neoplasms and prevent recurrence has not been well studied. Recent studies have reported that use of frozen sections has not led to improved disease outcomes for oral squamous cell carcinoma, so it is unclear whether the practice for benign neoplasms is helpful. Intraoperative radiographs of the resected specimen have been described in the literature to visualize bony lesions, but no data exist on the effectiveness of this method in predicting adequate resection margins. Specimen radiographs allow assessment of adequacy of the resection analogous to frozen section sampling from the excised specimen, which has been shown to improve local recurrence rates in oral squamous cell carcinoma. Previous histologic studies have suggested true margins of ameloblastoma extend 2 to 8 mm (mean, 4.5 mm) beyond the radiographic border of the tumor. Based on these data, 1-cm bony margins are recommended to allow a margin of safety to achieve negative final histologic margins. Concordance between measured radiographic margins and the final histologic margins also is not well known. The purpose of this study was to evaluate margin status and the utility of intraoperative margin assessments in resection of mandibular ameloblastomas. First, the relation of frozen section biopsy and intraoperative radiographic margin status to recurrence rate and final histologic margin size was assessed. Second, measured radiographic margins on the resected specimen were compared with quantified histologic margins. The authors hypothesized that frozen sections would not be necessary for resections planned for 1-cm margins and that the radiographic margins would be larger than the histologic margins. The specific aims were *1)* to compare recurrence rates when different intraoperative margin assessments were performed and *2)* to compare measured radiographic margins on an ex vivo specimen radiograph with the final histologic margins.
Methods: This was a retrospective cohort study of patients who underwent resection (≥1 cm) of mandibular ameloblastomas from 2005 through 2015. Patients were included if they had at least 1-year follow-up and complete records. Demographic variables included age, gender, and type of resection (segmental vs marginal). Predictor variables were type of margin assessment: *1)* frozen section, *2)* intraoperative ex vivo specimen radiograph, *3)* both, or *4)* none. The outcome variables were final margin status and recurrence rate. Accuracy of intraoperative radiographic margins was determined by comparison with histologic margin distance. Descriptive statistics were conducted with the Fisher exact test.

Results: The study sample consisted of 35 patients (47.5 ± 20.4 yr old; 16 men) who underwent 25 segmental and 10 marginal resections. Ten had frozen sections only, 3 had ex vivo specimen radiographs only, 10 had no intraoperative measurements, and 12 had both. There were no positive frozen sections. One patient had a positive posterior bony margin at final pathology despite negative frozen section histology. There was no difference in recurrence rate at latest follow-up among cohorts. The anterior radiographic margin was 11.8 ± 5.9 mm compared with 11.5 ± 7.5 mm by histology (P = .124). The posterior radiographic margin was 12.3 ± 5.3 mm compared with 9.8 ± 6.5 mm histologically (P = .546). Margin distances that were at least 5 mm when measured with specimen radiographs had histologic margin distances of at least 5 mm in 25 of 30 resection margins (83.3%). There was no difference in disease recurrence (no recurrences) between patients who had and who did not have the various combinations of intraoperative margin assessments at 1 year and at latest follow-up (range 1 to 11 years).
Conclusion: Resection of ameloblastoma with planned margins of at least 1 cm is sufficient to prevent recurrence of ameloblastoma. Achieving a radiographic margin of at least 5 mm provided a histologic margin of at least 5 mm 83.3% of the time.

Table 1. CHARACTERISTICS OF STUDY SAMPLE

	Type of Intraoperative Margin Assessment				
Variable	None (n = 10)	Frozen Sections (n = 10)	Ex Vivo Radiographs (n = 3)	Frozen Sections and Ex Vivo Radiographs (n = 12)	All Patients (N = 35)
Age (yr)	52.4 ± 19.7	45.5 ± 16.3	60.7 ± 21.9	41.7 ± 23.70	47.5 ± 20.4
Gender					
Men	7	3	2	4	16
Women	3	7	1	8	19
Type of resection					
Segmental	5	6	2	12	25
Marginal	5	4	1	0	10
Follow-up (yr) (min, max)	4.3 ± 3.1 (2, 10)	3.4 ± 2.9 (1, 11)	3.3 ± 1.2 (2, 4)	2.1 ± 1.2 (1, 5)	3.2 ± 2.5 (1, 11)
Frozen sections slides positive at anterior or posterior resection margins, n	N/A	0 of 23	N/A	0 of 20	0 of 43
Positive final histologic margins (yes)	0	1*	0	0	1*
Radiographic anterior margins (mm)	N/A	N/A	8.6 ± 4.1	12.6 ± 6.1	11.8 ± 5.8
Radiographic posterior margins (mm)	N/A	N/A	10.3 ± 2.5	13.0 ± 5.8	12.3 ± 5.2
Final histologic anterior margins (mm)	11.4 ± 8.4	9.0 ± 5.81	5.8 ± 5.3	14.3 ± 7.6	11.5 ± 7.5
Final histologic posterior margins (mm)	6.88 ± 5.8	11.8 ± 7.0	6.0 ± 7.1	11.5 ± 6.5	9.8 ± 6.5

Abbreviations: max, maximum; min, minimum; N/A, not applicable.
* One slide was positive on final pathology at the posterior bony resection margin.

Peacock, Ji, and Faquin. Confirming Margins When Resecting Ameloblastomas. J Oral Maxillofac Surg 2017.

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Improving Pediatric Preventive Services by Redefining Ambulatory Quality Metrics and Enhancing the Electronic Medical Record

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Introduction: In 2017, the Department of Pediatrics at Massachusetts General Hospital (MGH) changed quality measures from claims-based to clinically-based metrics monitored directly through the electronic medical record (EMR) with enhanced decision-support technology and comparable real-time data. A composite was developed to focus on age and/or gender-specific preventive services, which are in compliance with the American Academy of Pediatrics Periodicity and Early and Periodic Screening, Diagnosis and Treatment schedules and CDC guidelines. The composite encompasses six categories: immunizations, physical/sensory screenings, lab screenings, developmental/behavioral screenings, preventive services and asthma control. In addition, several measures include a secondary component to capture follow-up on abnormal findings (i.e.: vision, hearing and BMI screenings). By adopting clinically-based measures, integrating automated EMR tools and leveraging Pediatric Population Health Coordinators (PHCs), outcomes on preventive services are expected to improve; in addition to enhancing provider engagement in monitoring population health management efforts.
Methods: Several new EMR tools were implemented to support daily work. For example, SmartPhrases created to facilitate documentation and data capture, iPads programmed to administer Patient Reported Outcomes Measures (PROMs), and decision-support functionality enhanced to facilitate adoption, engagement and ease of revising workflows. PHCs will be responsible for ongoing patient panels monitoring and identifying patients coming due and overdue for services using EMR registries. PHCs will engage with providers to teach them to use new EMR tools, take actions on patients, and help practices develop systems improvement projects. Through the MGPO Quality Improvement Bonus Program, providers are incentivized to review data with practice leadership and PHCs to identify improvement areas and strategizing quality improvement efforts that are important to the practice. Performance on individual components during calendar year 2016 will be compared to rates during calendar year 2018, given that 2017 is a transitional and learning period. In addition, since many activities were not collected electronically previously, chart review will be required to compare 2016 performance.

Results: The patient population under age 22 in the composite is 42,778. Overall composite baseline performance as of July 2, 2017 is 36.1%. The following are baseline rates for individual components: --Immunizations for vaccines due before ages 2, 6 and 12-21: 62.6%, 61.4% and 71.2% respectively --Anemia screening: 94.3% --Lead screening: 93.9% --Chlamydia screening for sexually active adolescent females: 68.7% --Developmental/behavioral health screenings require use of new EMR tools. Previously collected screenings can only be identified via chart review; therefore true baseline performance for the composite is 0%. Each component of the composite is weighted equally. Total possible points for each patient will be determined by the number of measures the patient is eligible for based on age and gender at the time of measurement. For 2017, the target is a 1% improvement over baseline (to 37.1%) by December 31, 2017.
Conclusion: Changing quality metrics, enhancing EMR tools and engaging PHCs may improve preventive services for patients and improve individual provider engagement in quality improvement and population health activities.

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Development & Psychometric Evaluation of the Professional Practice Environment Inventory (PPWEI)

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Introduction: The Professional Practice Work Environment Inventory (PPWEI) is a new instrument within an evolving program of workforce evaluation research (Ives Erickson, Jones, Ditomassi, Duffy, 2004, 2009) that measures nine components of the practice environment: Autonomy /Control over Practice; Communication about Patients; Cultural Sensitivity; Handling Disagreement and Conflict; Staff Relations with Physicians, Staff and Hospital Groups; Sufficient Staff, Time and Resources for Quality Patient Care; Supportive Leadership; Teamwork; and Work Motivation. The instrument has been utilized with the following disciplines: physical therapy, occupational therapy, respiratory care, speech/language pathology, social work and chaplaincy. The purpose of this study is to evaluate the psychometric properties of the PPWEI.
Methods: The focus of this study was a psychometric evaluation of the 72-item PPWEI undertaken with 874 nurses providing direct care to patients at the Massachusetts General Hospital. Psychometric evaluation included (a) internal consistency reliability using Cronbach's alpha and item analyses; (b) Principal Components Analyses with Varimax rotation and Kaiser normalization procedures; and (c) Cronbach's alpha internal consistency reliability of resulting components. Cronbach's alpha reliability coefficients of PPWEI component subscales ranged from .82 to .93.
Results: The PPWEI is a 62-item psychometrically sound measure of nine professional practice environment components in the acute care setting and has sufficiently reliable and valid subscales for use in healthcare research.
Conclusion: For agencies pursuing or sustaining Magnet® recognition, the PPWEI is effective in measuring clinicians' ratings of their professional practice environment over time and is aligned with the 5 Magnet model components: transformational leadership; structural empowerment; exemplary professional practice; new knowledge, innovations, and improvements; and empirical outcomes. Through administration of the PPWEI over time, a greater understanding of organizational concepts that influence nurses and other disciplines' satisfaction with the professional practice work environment can be realized.

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Use Feasibility of a Continuous Temperature Monitoring Device (iThermonitor)

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Introduction: Fever is often the first sign of an underlying inflammatory process and one of the earliest indicators that alerts pediatric caregivers to seek medical attention. In children who have undergone chemotherapy or surgery, episodic monitoring of body temperature by caregivers has traditionally been the only option for early detection of fever. This adds significant burden to the already demanding process of taking care of a sick child. In this study, we test the usability and feasibility of *iThermonitor*, an innovative device that continuously monitors body temperature and automatically transmits the data wirelessly to mobile devices. The iThermonitor device enables caregivers to remotely view or track fever patterns and has the ability to detect and alert caregivers about out-of-range temperatures.
Methods: A dyad of 25 pediatric patients and their caregivers from the MGH Pediatric Surgery Department and the MGH & DFCI Pediatric Cancer Center were recruited to use the iThermonitor continuously for 14-days. Daily logs completed by caregivers were used to collect information regarding device usage. The primary outcome was the use feasibility of the device.

Secondary outcomes included usability, acceptability, satisfaction and engagement with the device, assessed through the end line surveys. The Generalized Anxiety Disorder-7 questionnaire was used to assess caregiver anxiety at baseline and closeout. **Results:** 19 participant dyads complete the study. Mean age of child participants was 9 years (±6) and 41 years (±7) for caregivers. 70% of the participants were undergoing chemotherapy and the remaining had undergone surgery in the period before enrollment. All 19 caregivers reported to have viewed temperature data on the study provided iPad tablet at least once per day, and more than a third did so 6 or more times per day. Caregivers of children undergoing chemotherapy were twice as likely to report viewing temperature data six or more times per day as compared to caregivers of children who had undergone surgery. 74% of participants reported experiencing an out-of-range temperature alert at least once during the study. 89% of caregivers were satisfied with the usability of the iThermonitor device and reported feeling more confident about monitoring temperature using the device. Almost 80% of the caregivers relied on the iThermonitor as their sole temperature-monitoring device during the study period. 79% of caregivers agreed that viewing measurements on the app was useful to better manage their child's health. 95% of the caregivers were assessed to have no or mild anxiety at the end of the study period, compared to 79% at the beginning (p=0.725). In qualitative feedback, caregivers reported poor attachment of temperature probe, limited range of wireless connection, low battery life and problems with device synchronization as areas for future improvement of the device. **Conclusion:** The iThermonitor is a highly feasible and easy to use device for continuous temperature monitoring in children. Improving upon select technical features may considerably enhance acceptability of and satisfaction with the device among caregivers.

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Sophia C. Kamran, Radiation Oncology

Genomic evolution and acquired resistance to pre-operative chemoradiation (CRT) in locally advanced rectal cancer

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Introduction: Pre-operative CRT is the standard for locally advanced rectal cancers. However, at the time of surgery, patients have mixed responses with approximately 20% achieving a pathologic complete response (CR) and 20-40% having little to no response (NR). Pathologic downstaging after CRT is associated with improved outcomes but molecular predictors of response are incompletely understood. The long-term goal of this project is to characterize somatic mutations and derive mutational signatures distinguishing CR vs NR through whole exome sequencing analysis in pre- and post-CRT samples. In addition, we seek to describe the evolution of mutational load in tumors undergoing CRT, which may have implications for the role of immune checkpoint inhibitor therapies.
Methods: Locally advanced rectal cancer patients treated with neoadjuvant CRT were identified. DNA extraction from clinical FFPE samples and whole exome sequencing was performed on pre- and post-treatment tumor and matched germline DNA followed by standard mutation analysis pipelines to identify somatic mutations, insertion/deletions, and copy number variations (CNV).
Results: We identified 40 pre- and post-CRT matched tumor samples from 20 patients. All were uniformly treated with pre-operative fluoropyrimidine-based CRT (50.4 Gy) followed by surgery within 8-10 weeks. Ten patients were classified as NR while 10 patients were partial or complete responders (PR/CR) at the time of surgery. In our initial cohort, all FFPE samples (n=24) were successfully sequenced and passed quality control metrics. Mean somatic mutational burden pre-CRT was 3.87 mutations/Mb (range, 2.25-8.43), which is consistent with prior reports for colorectal tumors. Unexpectedly, mean somatic mutational burden in the post-CRT samples was not increased (mean, 3.86 mutations/Mb; range, 1.74-8.96) even though 83% of samples were from potentially aggressive tumors harboring mutations in the *KRAS* oncogene. Among the NR cases, 71% had concurrent *KRAS/TP53* mutations. This observation is consistent with our recent findings on the radioresistance of this tumor genotype in lung and colon cancer patients, which confirms the usefulness of the current study cohort. Among NR, the most common *KRAS* mutation was G12V (57%). The mean number of "pre-only" mutations (private to pre-treatment tumor) and "post-only" mutations (private to post-treatment tumor) mutations is 64.6 (SD=48) and 46.6 (SD = 37.8), respectively. Intratumoral heterogeneity was defined as the proportion of mutations per pre-treatment tumor that were subclonal. Dividing the cohort above and below a cutoff of 40% of subclonal mutations, of the NR cases, high pre-treatment heterogeneity was present in 57%, with no significant association between pre-treatment heterogeneity and responders/nonresponders (Chisquare p=0.2). There are almost no shared subclonal mutations between pre-treatment and post-treatment tumors (median 1.5 mutations, 25^{th}-75^{th} percentile 0.75-25.25 mutations). There is a statistically significant difference between the number of inferred subclonal pre-treatment and shared, but not shared and post-treatment mutations (Mann-Whitney U p = 0.03, p = 0.16 respectively). When analyzing the frequency of indel changes between pre-treatment

and post-treatment tumor samples, there was no significant change (median change= (-)0.5, t-test=1), Preliminary CNV analysis showed no major chromosomal changes between pre- and post-CRT samples.
Conclusion: We have established feasibility and a pipeline for performing whole exome sequencing on FFPE pre- and post-CRT rectal samples. Our initial, *KRAS* mutation-enriched cohort demonstrates no significant change in mutational burden between pre- and post-CRT samples, suggesting that the evolution of treatment resistant subclones is not through hypermutation.

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Motohiro Kano, MD, Surgery - Pediatric

Concurrent MIS treatment during chemotherapy preserves the ovarian reserve and fertility

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Introduction: We have discovered that Mullerian Inhibiting Substance (MIS, also known as AMH) produced by granulosa cells of actively growing follicles of the ovary inhibits activation of the primordial follicle, the first irreversible step of folliculogenesis. One of the major causes of ovarian insufficiency is chemotherapy-induced over-activation, in which too many primordial follicles are activated. Toxicity to growing follicles compromise the negative feedback provided by endogenous MIS. We hypothesized that replacement with exogenous MIS can prevent ovarian insufficiency caused by chemotherapy and lead to viable offspring as documented by prolonged breeding studies.
Methods: To test this hypothesis, we pre-treated C57BL/6 mice (N=5/group) with intraperitoneal implantation of an osmotic pump delivering recombinant MIS during two cycles of doxorubicin (DOX; 6mg/kg IP/week). After improved follicle counts were demonstrated in the mice who received DOX and MIS, the animals were subsequently mated continuously for over five months and their fertility was monitored.
Results: Implantation of an osmotic pump delivering recombinant MIS intraperitoneally in C57BL/6 mice during two cycles of DOX resulted in a 2.9-fold ($p<0.001$) increase in primordial follicle counts compared to control mice receiving chemotherapy plus saline (Fig1. A). Subsequent breeding experiments revealed an increase in the cumulative number of pups compared to control mice receiving chemotherapy plus saline ($p=0.02$) (Fig1. B) and also resulted in a decrease of dystocia, a previously documented lethal complication of DOX treatment ($p=0.038$) (Fig1. C).
Conclusion: MIS protects the ovarian reserve by counteracting the over-activation and depletion of primordial follicles caused by chemotherapy-induced cytotoxicity to growing follicles. Prolonged breeding experiments show that MIS thereby preserves fertility. An unexpected salutary effect was found that MIS cotreatment also reduces the dystocia associated with DOX suggesting a protective effect to the uterus.

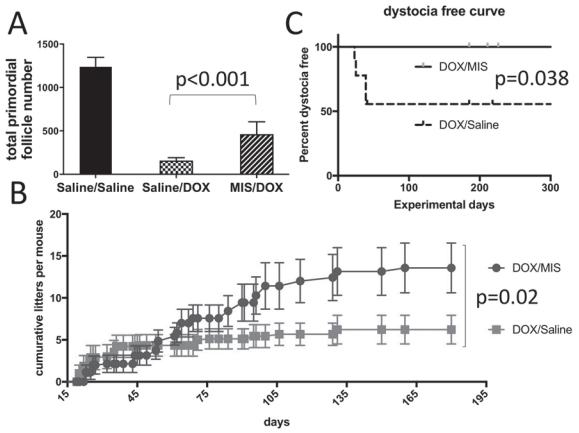

Fig1. Ovarian reserve and fertility of C57BL/6 mice treated with doxorubicin IP during MIS treatment.

C57BL/6 mice were implanted with Alzet™ osmotic pumps delivering MIS IP at 600ng/h (or saline) and treated weekly with doxorubicin (DOX; 6mg/kg). The mice were euthanized 7days after the 2nd injection of DOX or were placed in mating pairs which included one treated and one control female continuously housed together with a breeding male after a 2-week recovery period for 6 months. (A) DOX showed high toxicity to the primordial follicles and MIS protected the primordial follicle from depletion by 2.9-fold. p-value by two-way ANOVA test. (B) MIS treated mice had more total cumulative litters per female. p-value by Mann-Whitney test. (C) Dystocia was occurred in half of the control animals, whereas the mice treated with MIS did not experience dystocia. The plots indicate the occurrences of dystocia during the experiment. p-value by Chi-squared test.

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David L. Keefe, Medicine - Endocrine-Reproductive Endocrine

Evidence from Human Genetics and Zebrafish Modeling For Heterozygous Loss of Function Mutations in *TCF12*, a Basic Helix-Loop Helix Transcription Factor, as a Cause of Kallmann Syndrome and a Critical Role in GnRH Neuronal Ontogeny

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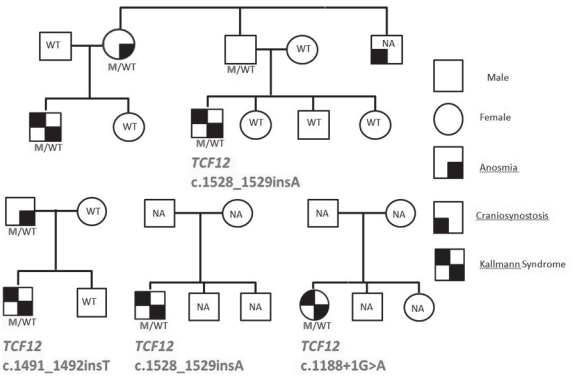
Introduction: Isolated gonadotropin-releasing hormone (GnRH) deficiency (IGD) is a rare Mendelian disorder 1:1:29,000 in males and 1:120,000 females characterized by a defective secretion or action of GnRH resulting in failure of puberty, hypogonadotropism and infertility. Approximately 60% of IGD patients exhibit anosmia, a phenotypic hallmark defining a subset of IGD referred to as Kallmann Syndrome (KS). While ~20 genes are known to cause KS, the genetic etiology in >50% remains unknown. Herein, we describe mutations in a transcription factor as a novel cause of KS thus providing the first human evidence for a critical role for a basic-helix-loop-helix protein in GnRH ontogeny.

Methods: The index family with two affected male cousins with KS who were negative for all known KS genes was referred to the Harvard Reproductive Endocrine Sciences Center for whole exome sequencing (WES). Putative causal genetic variant(s) emerging from this family-based analysis were then queried in our broader WES data available from >300 KS subjects participating in the Center's Genetics study at the Broad Institute. Variant calling and quality scores was performed using the GATK guidelines; jointly called VCF files were analyzed using GEMINI v. 0.19.1; variant annotation was performed with the Ensembl Variant Effect Predictor (VEP - GRC37/hg19 assembly). Rare sequence variants (RSVs) (<0.01 in gnomAD database) were analyzed for both autosomal recessive (AR) or dominant (AD) variants and were required to be have a quality depth >5 and be predicted as damaging by either Polyphen2 or SIFT. Variants in putative candidate genes emerging from the index Family were then queried using the GEMINI database for ascertaining additional discovery variants in the larger KS cohort.

Results: AR analysis failed to reveal a segregating variant, but AD analysis yielded 6 heterozygous RSVs shared by the cousins that were then prioritized using the gnomAD database to select for functional variation with a high constraint metric for either loss of function (pLI >0.9) or missense mutations (z score>3.0). These functional restraints yielded two RSVs (*SRCIN1 p.Glu1079Lys*;*TCF12* S509fs*18) with high likelihood of pathogenicity. The MAF of *SRCIN1* in gnomAD was 0.0006 whereas the *TCF12* frameshift was private to our index family. Sanger segregation of the *TCF12* RSV in the pedigree confirmed the variant in both cousins, the index patient's apparently unaffected father and the cousin's anosmic mother (paternal aunt of index case) but in no other family members. WES from 300 unrelated KS probands performed on that same Broad sequencing platform revealed 3 additional *TCF12* RSVs in *TCF12* (2 frameshifts and 1 canonical splice site) in 3 unrelated KS individuals who were also negative for all other known KS genes and all *TCF12* variants were novel (MAF in gnomAD:0) with incomplete penetrance (**Fig 1**). Overall, our KS cohort was significantly enriched for *TCF12* LOF RSVs compared to gnomAD using Fischer's exact test for rare variants ($p < 0.05$). Functional analysis using whole-mount Zebrafish MO and CRISPR/Cas9 embryos immunostained with a pan-GnRH antibody showed a reduction in the length of the developing terminal nerve, a region required for GnRH3 neurogenesis in zebrafish. In addition, the mutant zebrafish also showed absent/reduced/disorganized GnRH-GFP expression. Both the length of the terminal nerve and the GnRH-GFP expression were rescued by full length human WT *TCF12 mRNA*.

Conclusion: 1) Human genetic data and *in vivo* functional validation in zebrafish nominate high impact, LOF mutations in *TCF12* as a novel cause of an autosomal dominant of KS. 2) The incomplete penetrance of the *TCF12* LOF mutations reiterate the well established oligogenic basis of KS suggesting that identification of additional genetic modifiers will help facilitate the understanding of the complex genetic architecture of KS in humans. 3) These findings uncover a previously unknown but critical role for the bHLH transcription factors in the ontogeny of GnRH neuronal ontogeny and human reproduction.



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Tanya Keenan, MD, MPH, Medicine - Hematology/Oncology

Higher mutation burden and mutant allele fraction of circulating tumor DNA corresponds to worse progression free survival in metastatic breast cancer patients

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Introduction: Genomic profiling of circulating tumor DNA (ctDNA) allows non-invasive monitoring of tumor genetic changes and molecular heterogeneity. In addition to actionable mutations, mutational landscape derived from ctDNA could provide a better representation of overall tumor burden and tumor heterogeneity, as well as potentially impact clinical outcomes. To evaluate this hypothesis, this study assessed the association of mutation burden and average mutant allele fraction (MAF) with tumor subtype, therapeutic response, and survival in patients with metastatic breast cancer.
Methods: Whole blood samples from patients with metastatic breast cancer were collected during clinic visits before start of a new therapy. Plasma-derived cell-free DNA underwent complete next-generation sequencing of 73 cancer-related genes with the Guardant360 test. Mutation burden was defined as the number of genes with mutations, and average MAF was calculated as the sum of the highest MAF for each mutated gene divided by the number of genes with mutations. Time to progression was measured from the date of new treatment initiation after circulating tumor DNA collection to the date of progression. Multivariate cox proportional hazard models assessed the association of mutation burden and average MAF with progression free survival (PFS), adjusted for age, receptor subtype (hormone receptor positive, HR+; human epidermal growth factor 2 positive, HER2+; triple negative breast cancer, TNBC), treatment subtype (chemotherapy vs. targeted therapy), and number of prior metastatic breast cancer therapies. A p value of 0.05 was considered statistically significant.
Results: The study population consisted of 158 women with metastatic breast cancer (108 HR+, 14 HER2+, 19 TNBC) with a median age of 59 years and a median of 2 prior metastatic breast cancer therapies. Median follow up time was 4.0 months, and median PFS was 15.7 months. Mutation burden was greater in triple negative compared to hormone receptor positive breast cancer (7.5 vs. 4.8, p = 0.02) but no different in patients with > 2 prior metastatic therapies vs. not (5.1 vs. 4.7, p = 0.60) and age >45 vs. not (5.0 vs. 3.9; p = 0.26). In univariate models, high mutation burden (> median of 2) and high MAF (> median of 1.4) were significantly associated with worse PFS (Table). These results were similar in effect size and significance when adjusted for age, receptor subtype, treatment subtype, and number of prior metastatic breast cancer therapies. Impact of mutation burden on response to specific therapies will be presented at the meeting.
Conclusion: Higher ctDNA mutation burden and average MAF is associated with worse progression free survival and possibly reflects a more treatment refractory phenotype. Whether immunotherapy, alone or in combination, could influence the clinical outcomes in metastatic breast cancer patients with high ctDNA mutation burden is unclear and warrants additional research.

Variable	Hazard Ratio	95% Confidence Interval	p value
High mutation burden	1.99	1.12-3.54	0.02
High mutant allele fraction	1.88	1.06-3.33	0.03

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Freedberg Kenneth, Medicine - General Internal Medicine

The cost-effectiveness and budgetary impact of a dolutegravir-based regimen as first-line treatment of HIV infection in India

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Introduction: Dolutegravir (DTG)-based antiretroviral therapy (ART) is recommended for first-line HIV treatment in the US and Europe. Efavirenz (EFV)-based regimens remain the standard of care (SOC) in India. We examined the clinical and economic impact of DTG-based first-line ART in the setting of India's recent guidelines change to treating all patients with HIV infection regardless of CD4 count.

Methods: We used a microsimulation of HIV disease, the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)-International model, to project outcomes in ART-naive patients under two strategies: (1) *SOC*: EFV/tenofovir disoproxil fumarate (TDF)/lamivudine (3TC); and (2) *DTG*: DTG+TDF/3TC. Regimen-specific inputs, including virologic suppression at 48-weeks (*SOC*: 82% vs. *DTG*: 90%) and annual costs ($98 vs. $102), were informed by clinical trial data and other sources and varied widely in sensitivity analysis. We defined strategies as "cost-effective" if their incremental cost-effectiveness ratios (ICERs), measured in $/year-of-life saved (YLS), were <1x Indian annual *per capita* gross domestic product ($1,600 in 2015). We compared the budget impact and HIV transmission effects of the two strategies for the estimated 444,000 and 916,000 patients likely to initiate ART in India over the next two and five years.

Results: Compared to *SOC*, *DTG* improved five-year survival from 76.7% to 83.0%, increased life expectancy from 22.0 years to 24.8 years (14.0 years to 15.5 years, discounted), averted 13,000 transmitted HIV infections over five years, increased discounted lifetime care costs from $3,040 to $3,240, and resulted in a lifetime ICER of $130/YLS. *DTG* remained cost-effective as long as its annual cost was ≤$260/year. Over a two- or five-year horizon, total undiscounted outlays for HIV-related care were virtually the same for both strategies.

Conclusion: A generic DTG-based regimen is likely to be cost-effective and should be recommended for initial therapy of HIV infection in India.

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Yuhree Kim, MD, MPH, Dermatology

Association between serum vitamin D levels and opioid use disorder

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Introduction: Cutaneous ultraviolet (UV) exposure triggers the production of vitamin D in the skin and causes epidermal keratinocytes to synthesize proopiomelanocortin (POMC), which is processed to various biologically active peptides, including melanocyte-stimulating hormone and ß-endorphin. In rodents, UV exposure has been shown to produce opioid receptor-mediated addictive behavior driven by ß-endorphin. Clinically, vitamin D deficiency has been associated with chronic non-specific musculoskeletal pain syndromes and increased risk for pain. However, epidemiologic evidence associating vitamin D levels and opioid use is limited. We sought to examine the association between serum 25-hydroxyvitamin D (25(OH)D) levels and opioid use disorder following ten major surgeries using Optum data, which contains all inpatient, outpatient and pharmacy claims for over 55 million insured members in 50 states.

Methods: We identified members aged ≥18 years who underwent one of ten surgical procedures (CPT codes for total knee arthroplasty, total hip arthroplasty, laparoscopic cholecystectomy, open cholecystectomy, laparoscopic appendectomy, open appendectomy, cesarean section, functional endoscopic sinus surgery, cataract surgery, and transuretheral prostate resection) between January 2001 and December 2014 who had serum 25(OH)D levels measured in the 3 months before or after surgery. Patients with a history of prior opioid use disorder were excluded. Multivariable logistic regression analysis was performed to examine the association between serum 25(OH)D levels (deficient, <12; insufficient, 12-20; normal, ≥20 [ng/mL]) and subsequent diagnosis of opioid use disorder following surgery (ICD-9 codes), adjusting for age, sex and latitude of residence.

Results: A total of 1,989 members were identified; median age was 54 years and 73.8% were female. Approximately half of the members (47.4%) resided at latitudes above 37 degrees north. The majority of members (n=1,579, 79.4%) had 25(OH)D levels in the normal range, whereas 268 (13.5%) were in the insufficient and 142 (7.1%) in the deficient range. During a mean follow-up of 4.3 years, 12 patients (0.6%) developed opioid use disorder. Compared with patients with 25(OH)D levels in the normal range or in the insufficient range, those with 25(OH)D levels in the deficient range were more likely to be diagnosed with an opioid use disorder (0.4% vs. 1.1% vs. 2.1%, P=0.02). When adjusted for age, gender, and latitude of residence, patients with 25(OH)D levels in the deficient range demonstrated greater odds for opioid use disorder compared to those with 25(OH)D levels in the normal range (OR 5.71, 95% confidence interval [CI] 1.41-23.09; P=0.01), while patients with 25(OH) D levels in the insufficient range were not at increased risk of opioid use disorder (OR 3.00, 95% CI 0.74-12.05; P=0.12).
Conclusion: Low 25(OH)D levels were associated with higher risk of opioid use disorder among surgical patients. Assessment of serum 25(OH)D levels may provide information to identify patients with increased risk of opioid use disorder.

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Lauren N. Ko, B.A., M.Ed, Dermatology

Skin surface temperature detection with thermal imaging camera aids in the diagnosis of cellulitis

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Introduction: Cellulitis is a common skin and soft tissue infection (SSTI), often caused by streptococci or staphylococci. The incidence of cellulitis is approximately 200 cases per 100,000 patient years and accounts for approximately 2.3 million annual Emergency Department (ED) visits. Due to the lack of objective diagnostic tests, cellulitis is largely a clinical diagnosis, characterized by expanding, ill-defined redness, warmth, tenderness, and edema. However, many other skin diseases mimic the non-specific findings of cellulitis, including deep venous thrombosis (DVT), stasis dermatitis, and erythema migrans among others, collectively known as "pseudocellulitis". Skin warmth is a subjective and non-specific finding on which clinicians rely to diagnose SSTI. To date, there have been no prospective trials that use non-invasive thermal imaging to determine whether skin surface temperature aids in differentiating cellulitis from pseudocellulitis.
Methods: Chart review: Patient demographics were recorded. In the cohort randomized to dermatology consultation, diagnosis was determined by a board-certified dermatologist. In the cohort managed by standard of care, patients who were discharged with a diagnosis of cellulitis were categorized as having cellulitis, while those who were given an alternative diagnosis during hospitalization, discharge or <30 days of discharge were considered to have pseudocellulitis. Skin surface temperature: Within 24 hours of hospitalization, skin surface temperature was measured at the point of maximal temperature on the affected body part. Subsequently, unaffected skin surface temperature of the exact corresponding region of the contralateral body part was measured. In cases where affected skin was present bilaterally, unaffected skin surface temperature of the ipsilateral proximal extremity was taken. Measurements were taken with the FLIR© One thermal camera (Generation 1, FLIR Systems, Inc). The camera was held approximately 30 cm from the skin. Statistical analysis: All study data were securely collected and managed using REDCap Electronic Data Capture and analyzed using SAS 9.4. Logistic regression was used to developed predictive models using the imaging data of those randomized to dermatology consultation (n=40). We subsequently analyzed the ability of our predictive model to accurately predict the ultimate diagnosis of the cohort managed by standard of care (n=32).
Results: Of those evaluated by dermatology, 72% patients were diagnosed with cellulitis and 28% with pseudocellulitis. Cellulitis patients had an average affected skin temperature of 34.1°C, 3.7°C higher than the average corresponding unaffected skin area (95%CI:2.7-4.8°C, p<0.00001). Pseudocellulitis patients had an average affected temperature of 31.5°C, 0.2°C higher than the average corresponding unaffected area (95%CI:-1.1-1.5°C, p=0.44). Temperature differences between affected/unaffected sites were higher in cellulitis patients than in pseudocellulitis patients (3.7 vs. 0.2°C, p=0.002). Using a logistic regression model in the dermatology consult cohort, a skin temperature difference of ≥0.47°C conferred a sensitivity of 96.6%, specificity of 45.5%, PPV of 82.4%, and NPV of 83.3% for cellulitis diagnosis. This model was validated in the other cohort and correctly diagnosed 100% of cellulitis patients and 50% of pseudocellulitis patients.
Conclusion: Skin surface temperature differences are greater for cellulitis compared to pseudocellulitis. Using thermal imaging upon presentation to the ED, our predictive model accurately predicted 100% of cellulitis cases and identified 50% of pseudocellulitis cases that would have been misdiagnosed. Further multi-institution prospective studies are needed to validate these findings

Skin Surface Temperatures in Cellulitis and Pseudocellulitis Patients Randomized to Dermatology Consultation

	Affected skin temperature (°C)	Unaffected skin temperature (°C)	Difference, mean (95% CI) p-value
Cellulitis, Mean (95% CI)	34.1 (33.3 - 34.9)	30.4 (29.2 - 31.6)	3.7 (2.68 - 4.76) <0.00001
Pseudocellulitis, mean (95% CI)	31.5 (29.3 - 31.4)	30.4 (29.2 - 31.6)	0.2 (-1.07 - 1.49) 0.44425
Difference, mean (95% CI) p-value	2.6 (0.7- 4.6) 0.008	-0.9 (-3.3-1.6) 0.48	3.5 (1.9-5.2) 0.002

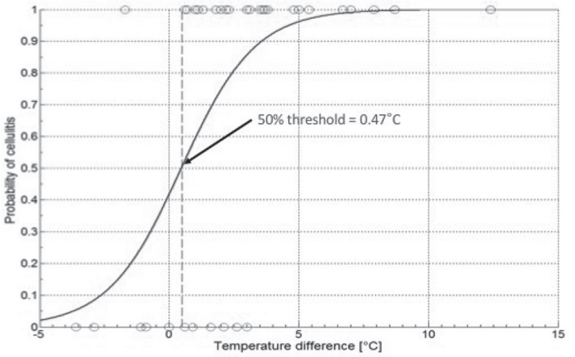

Figure 2. Predictive model. Using logistic regression in the cohort randomized to dermatology, we determined probability of cellulitis based on temperature difference between affected and unaffected skin. Red circles indicate cellulitis patients and green circles indicate pseudocellulitis patients.

Figure 1. Predictive model. Using logistic regression in the cohort randomized to dermatology, we determined probability of cellulitis based on temperature difference between affected and unaffected skin. Red circles indicate cellulitis patients, green circles indicate pseudocellulitis patients.

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Lauren N. Ko, B.A., M.Ed, Dermatology

The Effect of Dermatology Consultation On Outcomes of Patients with Presumed Cellulitis - A Randomized Control Trial

L.N. Ko[1,2], A.C. Garza-Mayers[1,2], J. St. John[2], L. Strazzula[2], P. Vedak[2], A.S. Dobry[1] and D. Kroshinsky[2,1]

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Introduction: Cellulitis is estimated to cost $3.7 billion in the United States annually. Previous literature has demonstrated a high misdiagnosis rate for cellulitis, leading to unnecessary antibiotic use and healthcare cost. With no accurate diagnostic laboratory or imaging test available, the proposed gold standard of cellulitis diagnosis is recognition by a dermatologist or infectious disease specialist, as recent studies have suggested that dermatologic involvement improves diagnostic accuracy of cellulitis. This study was designed to determine whether early dermatology consultation can improve treatment of hospitalized patients with suspected cellulitis and to determine if and how outcomes are affected. Improved recognition and treatment of this common infection could have significant impact on improved antibiotic stewardship, decreased widespread drug resistance, and most importantly, better patient outcomes.

Methods: Design: This randomized control study, conducted between 10/2012-01/2017 enrolled adult patients presenting to the emergency department with presumed diagnosis of cellulitis. Patients were randomized to the control group, which received the standard of care (i.e. treatment by primary medicine team), or the intervention group, which received dermatology consultation within 24 hours of hospitalization. Chart review of demographic information and hospital courses was performed. The main outcomes and measures were length of hospital stay and duration of intravenous antibiotic treatment. Secondary outcomes were analyzed and included: number of antibiotics used, clinical improvement at two weeks, and hospital readmission rate at one month. Moreover, the rate of pseudocellulitis was quantified in the intervention group **Statistical Analysis:** Sample size was based on a power calculation anticipating a 30% decrease in hospital stay or 20% IV antibiotic duration reduction in the intervention group, assuming a power level of 80% and alpha of 0.05. Data was analyzed using SAS9.4. Summary statistics were obtained for all variables. As appropriate, two-sided chi-square or Fisher's exact tests and t-tests were used to test whether variables were distributed differently between the two groups. A two-sided p-value<0.05 was considered significant.

Results: Length of hospital stay was not statistically different between the two groups. Sensitivity analysis revealed that duration of intravenous antibiotic treatment (<4 days: 86.3 versus 72.6%; p=0.04) and duration of total antibiotic treatment was significantly lower in patients who had early dermatology consultation (<10 days: 50.6 vs. 32.5%, p<0.01). Clinical improvement at 2 weeks was significantly higher for those in the intervention group (89.3 vs. 68.3%; p<0.01). There was no significant difference in 1-month readmission rate between the groups (4.5% vs. 6.9%, p=0.54). In the intervention group, the rate of cellulitis misdiagnosis was 30.7%. Among the entire cohort, 57.7% were treated with excessively long courses of antibiotics based on expert infectious disease guidelines. Dermatology's recommended treatment corresponded to the final treatment by the primary team in 69.3% of cases. Overall, 73.8% of dermatology consultations affected management in some way (i.e. wound care optimization, antibiotic coverage narrowing, concomitant fungal infection treated, etc.).

Conclusion: In this study, early dermatologic consultation was shown to increase patient improvement rates at 2 week follow up and to significantly decrease length of IV antibiotic use in hospitalized patients with presumed cellulitis. Dermatologists can improve outcomes in patients with suspected cellulitis by identifying alternate diagnoses, treating modifiable risk factors, and decreasing length of antibiotic treatment.

Sensitivity analysis comparing outcomes between patients who did and did not have an early dermatology consultation

Variable	Total (n=175)	No Early Dermatology Consultation (n=80)	Early Dermatology Consultation (n=95)	p-value
Discharged with antibiotics - N (%)				0.05
Yes	142 (81.1)	70 (87.5)	72 (75.8)	
No	33 (18.9)	10 (12.5)	23 (24.2)	
Length of Hospital Stay - N (%)				0.15
1 day	64 (36.6)	29 (36.3)	35 (36.8)	
2-3 days	59 (33.7)	22 (27.5)	37 (38.9)	
≥ 4 days	52 (29.7)	29 (36.3)	23 (24.2)	
Duration of IV Antibiotics - N (%)				0.04
0, 1 days	87 (49.7)	33 (41.3)	54 (56.8)	
2, 3 days	53 (30.3)	25 (31.3)	28 (29.5)	
≥4 days	35 (20.0)	22 (27.5)	13 (13.7)	
Number of Discharge Antibiotics - N (%)				0.06
0	33 (18.9)	10 (12.5)	23 (24.2)	
1	97 (55.4)	44 (55.0)	53 (55.8)	
≥ 2	45 (25.7)	26 (32.5)	19 (20.0)	
Total Duration of Antibiotic Treatment (Hospital + Home) - N (%)				<0.01
< 5 days	26 (14.9)	6 (7.5)	20 (21.1)	
5-9 days	48 (27.4)	20 (25.0)	28 (29.5)	
10-12 days	56 (32.0)	35 (43.8)	21 (22.1)	
≥13 days	45 (25.7)	19 (23.8)	26 (27.4)	
Patient's condition at 2 week follow-up - N (%)				
Improved	131 (78.9)	50 (66.7)	81 (89.0)	<0.01
Stable	25 (15.1)	18 (24.0)	7 (7.7)	
Worse	10 (6.0)	7 (9.3)	3 (3.3)	
Readmission with dx of cellulitis 1 month after discharge - N (%)				0.52
Yes	10 (5.7)	6 (7.5)	4 (4.2)	
No	165 (94.3)	74 (92.5)	91 (95.8)	

Based on Kruskal-Wallis test for continuous variables and two-sided chi-square or Fisher's exact test for other variables.

dx= diagnosis

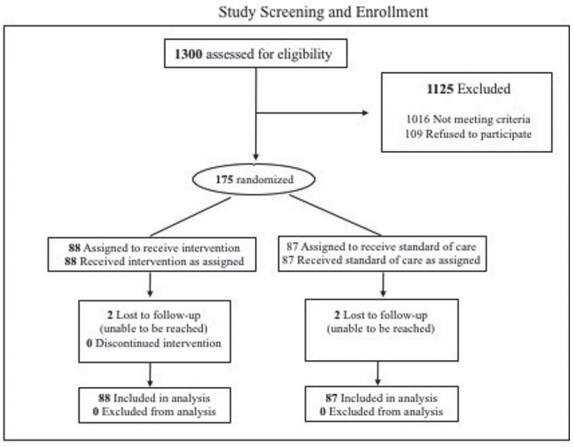

Figure 1: Study Screening and Enrollment

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Lauren N. Ko, B.A., M.Ed, Dermatology

Imaging and blood cultures are over-utilized despite their high cost and low clinical yield in evaluation of cellulitis

L.N. Ko[1,2], A.C. Garza-Mayers[2], J. St. John[2], L. Strazzula[2], P. Vedak[2], A. Dobry[2] and D. Kroshinsky[2,1]
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Introduction: Cellulitis is a commonly occurring acute bacterial skin infection leading to 650,000 cases resulting in U.S. hospital admissions annually. Cellulitis is considered a clinical diagnosis, with no gold standard laboratory or imaging modality available. In 2014, the Infectious Disease Society of America (IDSA) released evidence-based recommendations for the evaluation and treatment of cellulitis. These guidelines recommended against imaging except in cases of patients with febrile neutropenia, where imaging for deeper infection may be considered. In addition, blood cultures were only recommended in patients who had animal bites, were highly immunocompromised (i.e. malignancy on chemotherapy, neutropenia, immersion injuries), or who had signs of systemic toxicity. The goal of this retrospective study is to evaluate the clinical utility and cost of blood cultures and imaging in patients with presumed cellulitis.
Methods: This retrospective observational study enrolled 183 patients presenting to the Emergency Department (ED) with a presumed diagnosis of cellulitis between October, 2014 and February 2017. Following hospitalization, results of blood cultures and all relevant imaging studies were recorded. The timing of and rationale for obtaining computed tomography (CT) and magnetic resonance (MRI) imaging (via physician progress notes, discharge summaries, and radiology reports) was assessed and recorded. Using SAS 9.4 (SAS, Cary, North Carolina), the number of patients who underwent imaging and/or blood culture was quantified. The total number and types of imaging modalities for all patients was assessed, as was the rate at which each test changed management. Subgroup analysis comparing those who did and did not undergo testing (blood culture, imaging,) was performed, comparing patients' cellulitis risk factors, body temperature, and select serum biomarkers (glucose, white blood cell count [WBC], erythrocyte sedimentation rate [ESR], c-reactive protein [CRP], neutrophils, and eosinophil count) using Chi square analysis. Further, this study estimated the cost of diagnostic imaging and blood cultures based on annual cellulitis hospitalization rate and with the assumption that other academic medical centers order testing at a

similar rate as at this study site. The costs of diagnostic studies were determined using HealthCare BlueBook, a free online tool that calculates prices based on actual amounts paid on claims by health plans.

Results: Among 183 patients, median age was 58.1 years (interquartile range: 46.6-72.3), and 39.3% were female. Overall, 68% of the study population underwent ≥1 form of imaging, with 46% obtaining ultrasounds, 29% obtaining radiographs, 16% obtaining computed tomography imaging, and 6% obtaining magnetic resonance imaging. Radiologic imaging changed the management and/or diagnosis in 6.4% of patients who underwent scans. 33% of patients had blood cultures drawn, of which 1.7% were positive for microbial growth. Based on HealthCare Bluebook price estimates and cellulitis incidence, we estimate that the national annual cost of imaging ($127.4 million for ultrasonography, $14.9 million for radiograph, $15.2-27.1 million for CT, $64.5-117.2 million for MRI) and blood cultures ($4.9 million) for cellulitis patients is $226.9 million dollars in the United States.

Conclusion: Radiologic imaging and blood cultures have low clinical utility and portend significant cost in the evaluation and treatment of cellulitis. Imaging and blood cultures should be pursued only in patients who are severely immunocompromised or systemically toxic, or with in cases of high suspicion for deeper infection. Given high rates of pseudocellulitis, non-infectious etiologies should be considered among those who are not improving on antibiotics.

Table 1. The number of modalities and types of imaging obtained among study patients (n=183).

Modality of Imaging Obtained	N (%)
No imaging	59 (32.2)
Ultrasound only	48 (26.2)
X-ray only	23 (12.6)
CT only	12 (6.6)
Ultrasound + X-ray	17 (9.3)
Ultrasound + CT	7 (3.8)
Ultrasound + MRI	2 (1.1)
X-ray + CT	3 (1.6)
X-ray + MRI	1 (0.5)
Ultrasound + X-ray + CT	3 (1.6)
Ultrasound + X-ray + MRI	4 (2.2)
Ultrasound + CT + MRI	2 (1.1)
Ultrasound + X-ray + CT + MRI	2 (1.1)
Number of Imaging Modality Types Ordered	N (%)
0	59 (32.2)
1	83 (45.3)
2	30 (16.4)
3	9 (4.9)
4	2 (1.1)
Total Number of Imaging Tests	N (%)
0	59 (32.2)
1	76 (41.5)
2	24 (13.1)
3	16 (8.7)
4	6 (3.3)
5	2 (1.1)

CT= computed tomography

MRI= magnetic resonance imaging

X-ray = radiograph

Table 2. The number and percentage of study patients (n=183) receiving each modality of imaging and blood cultures, and the number and percentage of each type of test revealing a change in diagnosis.

Test	Total Tests Obtained	Tests Changing Diagnosis
Ultrasound - N (%)	85 (46.4)	1 (1.1)
Plain Radiograph - N (%)	53 (29.0)	1 (1.9)
Computed Tomography - N (%)	29 (15.8)	2 (6.9)
Magnetic Resonance - N (%)	11 (6.0)	4 (36.4)
Blood Cultures - N (%)	60 (32.8)	n/a
No growth	58 (96.7)	n/a
Growth	1 (1.7)	n/a
Undetermined	1 (1.7)	n/a

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Melissa Krystel-Whittemore, MD, Pathology

HER2 Testing in Breast Carcinoma: Comparison of Fluorescence In Situ Hybridization, Immunohistochemistry, and Next Generation Sequencing

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Pathology, MGH, Boston, MA, USA

Introduction: HER2 protein overexpression due to *ERBB2* gene amplification is seen in 10-20% of primary breast carcinomas. Treatment for these carcinomas is with targeted therapy such as Trastuzumab and others. HER2 testing is currently based on immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). Our study investigates an amplicon based sequencing technique (anchored multiplex PCR, AMP) to examine concordance rates of HER2 IHC and FISH testing with ERBB2 copy number variation (CNV) as examined with our institutional next generation sequencing (NGS) assay (SNAPSHOT). Additionally, we examined clinicopathologic data within the cohort.

Methods: 135 clinically annotated specimens from 127 patients with metastatic breast carcinoma were tested. The specimens analyzed by NGS included 38 metastases to the liver (28%), 17 to bone (13%), 16 to lymph nodes (12%), 15 to soft tissue (11%), 12 to lung (9%), 5 to brain and 5 to the gynecologic tract (4% each), as well as one metastasis to the orbit and the ileum (0.5% each). 25 samples were primary tumors of the breast (18%). HER2 IHC, FISH and NGS were performed on either formalin-fixed paraffin-embedded (FFPE) tissue blocks (n=96) or FFPE cytology cell blocks (n=39) using standard protocols

for HER2 IHC (Leica Bond automated IHC) and FISH (Vysis HER2:CEP17 Dual Color Probe). HER2 FISH was amplified if HER2:CEP17 ratio was 2 or greater, and equivocal if HER2 copy number per cell was 4 to 6. For NGS SNAPSHOT using the Ilumina platform, we determined the CNV relative log(2)ratios of 0.75-1 as borderline and >1 as amplified in *ERB-B2*. NGS testing failed in 8 specimens from 6 patients (5%) due to insufficient quality DNA.

Results: The patients' mean age at first diagnosis was 50 years (range 24-79) and mean age at NGS analysis was 57 years (range 24-81). Sixteen patients (12%) were HER2 positive, 109 (86%) HER2 negative, and 2 (2%) HER2 equivocal by IHC/FISH. ERBB2 gene amplification by NGS testing was positive in 13 patients (10%), negative in 110 (86%), and borderline in 5 (4%) (Table 1). Discordance between NGS results and IHC/FISH HER2 status was identified in 3 cases (2%): 1 patient negative by IHC/FISH with positive ERBB2 amplification by NGS, and 2 patients positive by IHC/FISH with negative ERBB2 amplification by NGS. 2 patients with equivocal HER2 IHC/FISH testing were negative by ERBB2 NGS, 2 patients positive by HER2 IHC/FISH were borderline by ERBB2 NGS, and 3 negative by HER2 FISH/IHC were borderline by ERBB2 NGS amplification.

Conclusion: The concordance rate for SNAPSHOT NGS with IHC/FISH was 98%. The overall sensitivity of ERBB2 NGS when compared with HER2 IHC/FISH testing was 86% with an overall specificity of 99%. Two patients with equivocal HER2 IHC/FISH amplification were negative by ERBB2 NGS and three patients negative for amplification by IHC/FISH were borderline by ERBB2 NGS amplification. NGS may be useful in HER2 testing of breast cancer and could help to identify patients that would or would not benefit from anti-HER2 therapy.

Concordance between the combined HER2 IHC/FISH and ERBB2 NGS

	Positive	Equivocal/Borderline	Negative	Total
HER2 IHC/FISH	16 (12%)	2 (2%)	109 (86%)	127
ERBB2 NGS	13 (10%)	5 (4%)	110 (86%)	127

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Miranda Lai, B.S, Radiology

Benefits of Utilizing a Centralized Tumor Metrics Service for Oncology Clinical Trials

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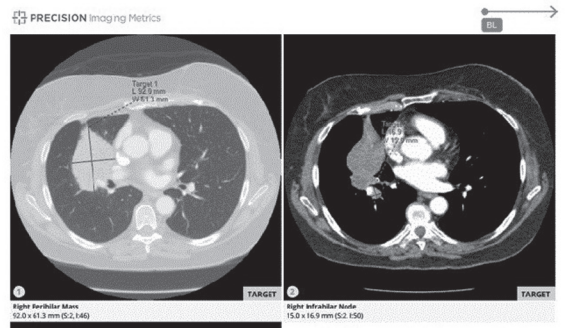
Introduction: Managing oncology clinical trials can be challenging, especially with the increasing complexity of protocols and imaging response criteria. Providing accurate measurements of tumor burden in time for the patient's visit is one of the most difficult tasks for cancer sites. With over 20 different response criteria in use, it can be difficult to understand and correctly apply each one without adequate training. Many cancer centers still manually track tumor measurements on Microsoft Excel, leading to inconsistent and incomplete documentation that is subject to human error. Therefore, it is difficult for sites to prepare for monitoring visits, data locks, and audits due to missing data and lack of image-based records. These challenges demonstrate a need for a centralized service to provide high quality reviews, with a quick turn-around time, and consistent tumor metrics data.

Methods: The Tumor Imaging Metrics Core (TIMC) was established in 2004 to provide centralized image review services for patients enrolled in clinical trials at the Dana-Farber/Harvard Cancer Center. To support this service, the TIMC developed a web-based workflow and data management system, branded Precision Imaging Metrics (PIM). The system allows TIMC to improve turn-around time by allowing clinical trial teams to make requests for tumor metrics and view finalized results on-line. Every day at least two scheduled radiologists review the imaging study measurements through the web application. The team of dedicated and experienced image analysts and radiologists are trained and certified as proficient in assessing established response criteria. Conformance checks for response criteria are built into the website to improve protocol compliance. Annotated, longitudinal image records are available as part of the standardized reporting to improve efficiency in preparing for audits (Figure 1). All results are locked and final after review. If any changes are made, trial staffs are informed and consulted via a re-review process.

Results: During the past year, TIMC processed 12,520 time points. Of those timepoints, 45% required results within the same day. Overall, 84% of the scans were provided on time with 96% of results provided within one hour of the requested due date (Figure 2). Only 143 of tumor metrics requests were questioned by the treating team or oncologist and sent for re-review by a second radiologist. Additionally, an in-house study of inter-rater reliability among image analysts resulted in a reliability coefficient of 0.94. Prior to the establishment of TIMC, it was reported that clinical trial staff took one to two weeks on average to prepare for audits. With the TIMC system, limited preparation is necessary for clinical trial staff due to the standardized reporting with annotated images.

Conclusion: Using a team of expert image analysts and radiologists, the TIMC has been able to provide rapid, reliable, and trackable results for tumor metrics despite the increased complexity of response criteria through standardized criteria training and streamlined workflows. Sponsors and oncologists can improve clinical trial management and benefit from the potential cost savings and increased efficiency through TIMC.



#	Label	Target	Assessment
1	Right Perihilar Mass	Y	92.0 x 61.3 mm (S:2, I:46)
2	Right Infrahilar Node	Y	15.0 x 16.9 mm (S:2, I:50)
3	Mediastinal	N	NM (S:2, I:32)
	IRRC		5893.1
	% change from Baseline		.0%
	% change from Nadir		.0%
	% change from Prior		.0%
	Response		BL
	Comments		Baseline iRC.

Figure 1: Printable TIMC Reports- Annotated Images and Standardized Reports

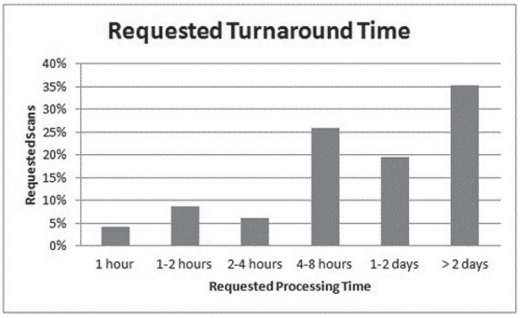


Figure 2a displays the amount of time requested to provide finalized results within TIMC business hours. A total of 12,520 timepoints were ordered between July 1, 2016 to June 30, 2017.

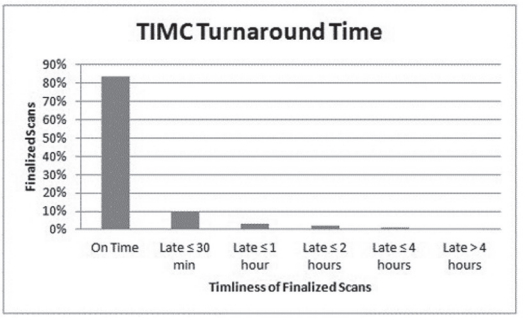


Figure 2b displays the timeliness of finalized results of the 12,520 time points processed between July 1, 2016 to June 30, 2017.

Figure 2: TIMC Turnaround Time

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Lauren M. Laifer, BA, Psychiatry

Parenting Sense of Competence Mediates the Relationship Between PTSD Symptoms and Family Functioning in Treatment-Seeking Post-9/11 Veteran Parents

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Introduction: Over 2 million service members have deployed in support of the post-9/11 conflicts, with research indicating that deployment-related disorders such as posttraumatic stress disorder (PTSD) may be associated with decreased parenting efficacy and satisfaction and subsequent child adjustment difficulties (see Gewirtz, Polusny, DeGarmo, Khaylis, & Erbes, 2010). However, limited data is available on the association between PTSD symptoms and family functioning in post-9/11 veterans.

Methods: As part of their clinical intake evaluation, 192 treatment-seeking post-9/11 veteran parents (91% male; *M* age = 37.2, *SD* = 9.3) completed the PTSD Checklist (PCL; Weathers, Litz, Herman, Huska, and Keane, 1993), the Parenting Sense of Competence Scale (PSOC; Johnston & Mash, 1989), and the General Functioning subscale of the Family Assessment Device (FAD; Epstein, Baldwin, & Bishop, 1983). Utilizing an IRB-approved de-identified data repository, we examined the association between PTSD symptom severity, PTSD symptom clusters, and family functioning in our clinical sample of veterans.

Results: There was a trend towards significance for the association between PTSD symptoms and family functioning ($r = 0.120$, $p < .10$), with follow-up analyses revealing that the numbing/avoidance symptom cluster (PCLc) was significantly associated with FAD ($r = 0.199$, $p < .01$). There was a strong negative correlation between parenting sense of competence and

family functioning (r = -.520, p < .001), such that veterans with higher scores on the PSOC reported lower levels of family dysfunction. Gender was not significantly associated with PCLc, FAD, or PSOC. A multiple regression analysis confirmed that PCLc was independently associated with FAD (F(1, 190) = 7.81, p < .01, R^2 = .040; β = .199, p < .01). When adding PSOC to the model, the model remained significant (F(2, 122) = 23.16, p < .001, R^2 = .275), and FAD was significantly associated with PSOC (β = -.505, p < .001) but not PCLc. Examination of the indirect effect of PSOC on the association between PCLc and FAD based on 4,000 bootstrapped samples (Preacher & Hayes, 2008) revealed a significant indirect effect (point estimate = 0.0092; bias-corrected and accelerated 95% CI = 0.00168, 0.0180).
Conclusion: Our results suggest that parenting sense of competence may play a role in mediating the relationship between PTSD symptoms and family functioning. Future interventions targeting parenting practices may dampen this relationship.

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Jacqueline Lane, PhD, Anesthesia, Critical Care and Pain Medicine

Self-reported sleep traits share common genetic architecture with psychiatric disorders and migraine

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Introduction: Sleep and circadian disruptions are often comorbid with brain disorders, but whether this is due to shared genetic etiology is unclear. To systematically study the genetic links and highlight potential causal relationships, we performed genetic correlation studies of sleep/circadian traits with psychiatric traits.
Methods: We performed a systematic study of genetic correlation between recent GWAS for correlated sleep traits, including self-reported sleep timing, quality, and quantity from adults aged 39-70 in the UK Biobank (N = 14 traits) and the most up-to-date GWAS for 24 neurological and psychiatric disorders from the Brainstorm consortium using linkage disequilibrium score regression (LDSC). For each study we conducted pair-wise correlation analysis using LDSC version 1.0.0 using all common SNPs from the HapMap3 panel from each of the summary statistics sets. We estimated the threshold of statistical significance as p=0.000214 using Bonferroni correction for 233.6 tests (for 14 independent circadian phenotypes and 16.6858 independent Brainstorm phenotypes). The number of independent tests was assessed using matrix decomposition of the genetic correlation results using matSpD, due to the correlated nature of some of the traits and phenotypes.
Results: Analysis of genetic correlation between 14 self-reported sleep traits and 24 psychiatric and neurological disorders identified significant correlations to schizophrenia, major depressive disorder, migraine, autism, ADHD and bipolar disorder. ADHD had significant correlation to both daytime napping and insomnia but not to sleep duration. Autism was significantly correlated only to extremes of chronotype. Both bipolar disorder and schizophrenia were positively correlated with sleep duration and sleep duration in males, but schizophrenia was additionally correlated with hypersomnolence, highlighted by correlations to long sleep (>8 hrs vs 7-8 h; r_G=0.363, p=8.55x10^{-7}), increased frequency of daytime naps (r_G=0.160, p=1.00x10^{-4}), and difficulty waking up in the morning (r_G=-0.284 to ease of waking up, p= 1.27x10^{-13}). The strongest correlations overall were observed for major depressive disorder, suggesting robust links to a number of sleep phenotypes. Significant correlation observed to insomnia (r_G=0.462, p=3.06x10^{-24}), difficulty of waking up in the morning (r_G=-0.403 to ease of waking up, p=7.49x10^{-19}) and excessive daytime sleepiness (r_G=0.226, p=5.72x10^{-5}), as well as interestingly to both short sleep duration (<7hrs, r_G=0.347, p=3.44x10^{-10}) and long sleep duration (>8 hrs, r_G=0.449, p=1.42x10^{-6}), likely implying a U-shaped relationship as well as a disparity between amount of sleep needed and received. In contrast, there was limited genetic correlation between sleep traits and neurological disorders, except for the striking shared heritability of insomnia symptoms with migraine and migraine without aura (r_G=0.322, p=8.07x10^{-13} and r_G=0.329, p=1.16x10^{-6} respectively) and between migraine and short sleep duration (r_G=0.200, p=4.65x10^{-5}). Interestingly, while sleep and circadian disturbances are common in Alzheimers disease, Parkinsons disease and MS, there was no evidence of common underlying biological pathways. Additionally, we find a genetic link between both sleep and circadian traits with subjective well-being, neuroticism and years of education. We also estimated the amount of phenotypic variance explained by shared genetics for brain disorders with significant correlations with one or more sleep traits, ranging up to 2.86% of brain disorder variance explained by genetics of a sleep trait (MDD variance explained by genetics of insomnia symptoms), and up to 3.38% of sleep trait variance explained by genetics of a brain disorder (long sleep duration explained by genetics of schizophrenia).
Conclusion: In this study we are able to confirm substantial shared genetic risk between sleep traits and neurological and psychiatric disorders, which mirrors the observed epidemiological associations in the literature. We observe specific and reasonable patterns of sleep traits associated with psychiatric disorders. This study underscores the presence of common neurobiological processes, perhaps related to the common neurotransmitter systems and regulatory pathways. This direct biological connection between sleep and psychiatric traits holds promise to discover new causal pathways and treatment avenues.

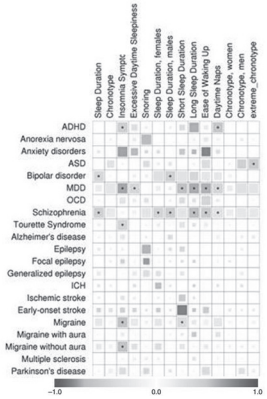

Figure 1. **Genetic correlations between sleep and psychiatric/neurological disorders.** Genetic correlation (rg) using LD score regression. The color scale represents the strength of correlation.

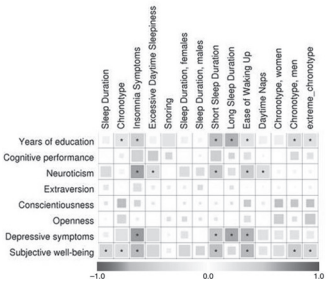

Figure 2. **Genetic correlations between sleep and neurological traits.** Genetic correlation (rg) using LD score regression. The color scale represents the strength of correlation.

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Jonathan Lans, Orthopedics

Open Reduction and Internal Fixation of Radial Head Fractures: Screws or Plates?

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Introduction: It is unclear what factors are associated with reoperation after open reduction and internal fixation (ORIF) of radial head and neck fractures. We evaluated what patient-, fracture- and treatment characteristics were associated with reoperation after radial head ORIF.

Methods: We retrospectively identified all patients that underwent primary ORIF of a radial head fracture using Current Procedural Terminology codes. All adult patients that were treated between 2002 and 2015 at a single institutional system were included (n=108). A medical chart review was performed to collect data regarding demographics, fracture- and treatment characteristics along with postoperative complications and indications for reoperation. There were 2 (3.3%) Mason I fractures, 21 (34.4%) Mason II fractures, 23 (37.7%) Mason III fractures and 15 (24.6%) Mason IV fractures. Most of the patients underwent screw fixation (75.9%), 24 of the patients had plate fixation and 2 patients had other types of fixation (Kirschner wire and suture fixation). All explanatory variables with a *p*-value <0.10 were included in a multivariate logistic regression.

Results: The reoperation rate after radial head ORIF was 22.9% (25 of 109) during a median follow-up of 6.9 months (IQR 2.9 – 13.8). After adjusting for fracture type (radial neck fracture versus radial head fracture), plate fixation was found to be an independent predictor for reoperation compared to screw fixation (OR 5.19, 95% CI: 0.093-0.32, p=0.004). Implant irritation was the leading (59.3%) cause for reoperation, followed by restricted motion (30%), heterotopic ossification (14.8%), pain (11.1%) and infection (7.4%).

Conclusion: Although plate fixation may be feasible for radial head fractures, this technique increases the odds of reoperation by 5 compared to screw fixation. When choosing fixation techniques, it may be preferable to perform fixation with only screws when possible.

Table 1: Bivariate Analysis Factors Associated with Reoperation Radial Head Fractures

Characteristic	Reoperation		*P-value*
	yes (n=25)	no (n=84)	
Age, median (IQR)	40.7 (27.5-54.0)	39.3 (28.3-53.8)	*0.63* [2]
Male, n (%)	11 (18.0)	50 (82.0)	*0.18**
Right, n (%)	10 (18.9)	43 (81.1)	*0.37**
Radial neck fracture, n (%)	4 (50.0)	4 (50.0)	*0.079**
Mason Classification, n (%)			*0.21**
I	0	2 (100)	
II	6 (28.6)	15 (71.4)	
III	8 (34.8)	8 (34.8)	
IV	1 (6.7)	1 (6.7)	
Surgery, n (%)			***0.001****
Screws	12 (14.6)	70 (85.4)	
Plate	12 (48.0)	13 (52.0)	
Other	1 (50.0)	1 (50.0)	

[1] n=61

[2] Using Mann-Whitney U test

* Using Fisher's exact test

Table 2: Multivariable logistic regression reoperation

Variable	Odds Ratio	Standard error	95% Confidence Interval	*P* Value
Radial neck fracture	1.13	0.97	[0.21, 6.1]	0.89
Plate fixation	5.19	3.0	[0.093, 0.32]	**0.004**

Area under the receiver operating characteristic curve = 0.67

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Logan D. Leathem, Psychiatry

The neural basis of generalization of fear and safety signals and alterations in these processes in subthreshold psychosis

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Introduction: Despite many decades of research, the neurobiological mechanisms that are altered in individuals with psychotic disorders such as schizophrenia remain unknown. However recent advances in human neuroscience and neuroimaging have provided insights about normal brain function that may facilitate a more mechanistic understanding of neuropsychiatric syndromes such as psychosis. One example of this progress is the recent increase in understanding of fear learning and memory mechanisms in humans. Recent studies have suggested that these mechanisms may be altered in individuals with psychosis; patients with psychosis exhibit abnormal fear perception and memory processes, as well as deficient "safety signaling," which is particularly prominent in patients with active delusions. However, the core abnormality underlying these deficits may be a more basic perceptual-emotional memory process that plays a role in both fear and safety signaling. Fear generalization is defined as the process of having a fear response to a stimulus that is similar, but not identical, to an aversive, threatening stimulus. Analogously, generalization of safety signals involves the absence of fear in response to a stimulus that is similar, but not identical, to a stimulus that has been established as safe. Under- or over-generalization of fear or safety signals could account for the subtle misperceptions experienced by psychotic individuals that over time could be misinterpreted and become delusional ideas. Thus, based on prior evidence for fear processing abnormalities in psychosis and this model, we have conducted several studies of fear generalization in healthy subjects and one in patients with schizophrenia. We demonstrated deficient fear generalization in the schizophrenia patients suggesting that the immediate retrieval of fear memories may be impaired in schizophrenia and contributes to psychotic states. However, because the majority of individuals with schizophrenia are chronically treated with antipsychotic medications (dopamine receptor antagonists) that suppress fear learning, we have begun to study fear generalization in individuals with subthreshold psychotic symptoms. It has been shown that these individuals frequently have abnormalities in brain and cognitive function similar to those observed in schizophrenia and share many demographic characteristics and risk factors with schizophrenia patients. This body of work supports the notion of a biological continuum between subthreshold and clinical psychosis. Thus, in the current study, to extend our findings in schizophrenia, we tested the hypothesis that generalization of fear and/or safety signals is deficient in individuals with subthreshold psychotic symptoms.

Methods: Forty-five participants underwent a Pavlovian fear-conditioning and generalization procedure, modified from Holt et al, 2014, while fMRI data and skin conductance responses (SCR) were simultaneously collected. During conditioning, two distinct face stimuli were shown. One face (CS+) was followed by an electrical shock, and the other (CS-) was not. The conditioning phase was followed by a generalization phase, during which the CS+ and CS-, as well as 8 facial morphs between the CS+ and CS-, were shown to the participants. Selected based on the subject's ability to discriminate between the two faces, the 8 morphs included stimuli below the subject's perceptual discrimination threshold. Following the scan, subjects rated how likely it was that each stimulus had been followed by a shock during the experiment.

Results: As a group, the participants exhibited significant generalization of conditioned fear responses, as manifested in the SCR and explicit ratings data, i.e, they showed greater fear responses to CS+-like stimuli in comparison to the neutral stimuli (the CS- and CS- like stimuli) (F =2.98, p=0.033 and F=73.33, p<0.001, respectively). Generalization of responses to the CS-, i.e., generalization of the safety signal, was also observed to stimuli that were perceptually indistinguishable from, or distinguishable but similar to, the CS-. Moreover, analyses of the fMRI data (conducted using independently-defined, *a priori* regions-of-interest and analyses of variance) revealed both significant fear and safety generalization in the anterior insula (right: F=4.74, p=0.001; left: F=4.03, p<0.001). Lastly, when we tested for the predicted reduction in generalization in participants with subthreshold psychotic symptoms, we found that those subjects showed reduced magnitudes of fear and safety generalization, compared to those without subthreshold psychotic symptoms. Moreover, in the whole cohort, the severity of these symptoms was negatively correlated with the magnitude of generalization responses of the left anterior insula (rs all < -0.37, ps all < 0.05).

Conclusion: Using individually-defined stimulus parameters, generalization of fear and safety signals in humans can be reliably and quantitatively measured using neurophysiological and behavioral methods. Using this approach, we found evidence that subthreshold psychotic symptoms are associated with impairments in the generalization of fear and safety signals, extending our observations in schizophrenia patients. We interpret these findings as suggesting that a decreased ability to generalize responses across perceptually similar stimuli could lead to the production of aberrant novelty signals and, in turn, the mis-assignment of salience to benign or irrelevant information. Follow-up studies will be necessary to identify the precise sequence of physiological events that could lead to subtle changes in fear and safety signal processing, which then may contribute to the emergence of psychotic symptoms in vulnerable individuals.

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Lauren Leavitt, MA, Medicine - General Internal Medicine

Improving Skills to Encourage Patient Involvement in Decision Making: Conducting Shared Decision Making Conversations

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Introduction: Shared Decision Making (SDM) is an approach to involving patients in medical decisions that is appropriate when clinical evidence supports more than one approach to care. The goal of SDM is to ensure that patients are well informed and receive treatments that match their goals and preferences. Patient decision aids (DAs) have been shown to support SDM, and Partners Healthcare System (PHS) has supported access to high quality DAs for common medical tests and treatments. However, decision aids alone are not sufficient to ensure SDM. Clinicians and staff need to develop specific communication skills to discuss evidence-based information about treatment options and outcomes, explore patient's goals and preferences, and determine the best treatment for each patient. The Health Decision Sciences Center (HDSC) team has delivered in-person SDM training sessions to hundreds of doctors, nurses, residents, clinic staff, and medical students. The trainings combine several different approaches including some didactic presentation, review of decision aids, interactive cases, and critique of video-based simulated patient interactions (SPI). Generally, participant evaluations of the in-person training sessions have been strong, and have been associated with increased use of DAs. The purpose of this pilot study was to assess the feasibility and acceptability of different approaches to SDM skills training for licensed clinicians that would be scalable for dissemination across PHS and to examine the impact on physicians' communication skills via simulated patient interactions.

Methods: The study recruited a convenience sample of active clinicians across PHS into a 2X2 factorial design. Participants were assigned (1) to review a webinar or three DAs, and (2) to receive feedback on their SPI or not. The SPIs were setup as a follow up phone call to discuss one of 3 topics: a new diagnosis of depression, sciatica due to herniated disc, and lung cancer screening for a current smoker who meets the criteria. The SPIs were transcribed and coded for the presence/absence of 9 key elements of SDM using Braddock's Informed Decision Making (IDM) framework (total scores ranged from 0-9). Study activities included baseline survey, first SPI, assigned intervention, second SPI and an exit survey. The surveys assessed confidence in SDM skills, satisfaction with the skills training, and the exit survey also assessed the amount of training completed. We examined whether results were different from our target response rate of 60% and completion rate of 70% using non parametric, single sample binomial test, and we calculated the effect size for change in IDM scores before and after training, and across study arms.

Results: The majority of interested clinicians 23/34 (68%) completed the baseline questionnaire and were enrolled (not different from target of 60% p=0.2). Participants were mostly primary care physicians (60%), female (65%) with a median of 11-20 years in practice. Overall 16/23 (70%) participants completed all evaluations (both SPIs and both surveys) and were included in the analyses (not different than our target of 70% p=0.6). The average Braddock IDM score was 3.9 (SD1.6) at baseline and 5.9 (SD1.6) after training (paired t-test $p<0.001$; and Cohen's d effect size estimate=1.2). Physicians in both the webinar and DA groups showed improvement in their SDM skills (mean difference 2.2 (SD1.8) for webinar and 1.6 (SD1.6) for DA p=0.5; Cohen's d effect size estimate=0.4). After completing the training more physicians were extremely or very confident in their ability to communicate risks and benefits to their patients (75% after vs. 53% before), in their ability to communicate the likelihood and probability of risks and benefits (63% after vs. 41% before), and in their ability to elicit patient preferences (56% after vs. 41% before). When asked to identify the most valuable part of the training, 8 of 16 participants identified the SPI practice, 4 from the webinar group stated the video presentation of a good SDM conversation in the webinar, and 3 from the DA group stated the material in the DA was most helpful. One participant said both the webinar and SPIs were most valuable.

Conclusion: This pilot provided important evidence of the feasibility of recruiting physicians for SDM skills training and of using SPIs for evaluation. This training approach, and in particular, the simulated patient interactions, was found to be a feasible and acceptable method of enhancing communication skills. Opening up the training to more clinicians and examining whether the results found with the SPIs are translated into routine practice with patients is an important area for further study.

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Oshrit Lebovitz, M.D, OB/GYN

Predictors of reproductive outcome following myomectomy for intramural fibroids

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Introduction: Fibroids are the most common benign tumor found in women of reproductive age. Their presentation is heterogeneous and can have an unfavorable impact on fertility, with 2-3% of infertility cases attributed to the effects of fibroids. Uterine fibroids are classified according to their location in the uterus: submucosal (SM), intramural (IM) and subserosal. While the effect of SM fibroid on infertility is well established, less is known regarding the role of IM fibroids on reproductive outcomes, and as such, the efficacy of myomectomy procedures to imprive infertility due to fibroids is controversial. This study aims to identify factors affecting reproductive outcomes among infertile women undergoing myomectomy for IM fibroids.

Methods: A retrospective cohort study included 112 infertile women who underwent myomectomy due to IM fibroids as part of treatment aimed at improving their fertility prospects. Reproductive outcomes were abstracted by reviewing the patient's medical records.

Results: Following myomectomy, conception rate was 42.8% (n=48). Women who concieved following myomectomy were significantly younger (36.5±4.1 years vs. 38±4.5 years; $p \leq .007$), and were mostly Caucasian (56% vs. 25% $p \leq .001$). In addition, patients who conceived had larger fibroids demonstrated in preoperative imaging (7 cm vs. 6 cm; $p \leq .009$), with fewer cases of cavity entry during surgery (13% vs. 28%; $p \leq .04$), and lower surgical complications rate (8% vs. 25%; $p \leq .02$). Multivariate logistic regression models identified patient's race as the only significant determinant of reproductive outcome when controlling for potential covariates. African –American women were much less likely to conceive following myomectomy compared to their Caucasian counterparts (OR .20; 95% CI .08-.74, $p \leq .01$).

Conclusion: Patient's race plays a significant role in the reproductive outcome of infertile women undergoing IM fibroid myomectomy as part of fertility enhancement. Physicians should consider racial disparities in outcomes when counseling patients regarding their probability of conceiving following myomectomy.

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Erik G. Lee, Bachelor of Science, Psychiatry

Functional Connectivity with Transcranial Magnetic Stimulation Reveals Default Mode Network Mechanisms of Depression

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Introduction: Transcranial magnetic stimulation (TMS) is a painless, focal, and noninvasive tool for inducing long-term neuromodulatory effects, that is approved by the Food and Drug Administration (FDA) for the treatment of major depressive disorder (MDD). This treatment utilizes targeted stimulation over the dorsolateral prefrontal cortex (DLPFC), taking place over the course of weeks, and resulting in an upregulation of functional activity at the site of stimulation. TMS has emerged as one of the most effective treatments for MDD, but our understanding of how TMS alters connectivity between functional networks, and the mechanisms of associated antidepressant response remain unclear. In this work, the authors explore measures of functional connectivity before and after TMS treatment, and evaluate how both baseline levels of connectivity, and changes in connectivity that occur throughout the course of TMS, are related to antidepressant response.

Methods: A total of 17 patients were stimulated with TMS over the left prefrontal cortex for the treatment of MDD (median number of treatments = 36). Resting state functional magnetic resonance imaging (fMRI) was employed before and after the full course of TMS to measure functional connectivity. Each subject had two resting state scans at both visits (TR = 3 s, Voxel Size = 27 mm^3 Timepoints = 124). The location of the stimulation site used for treatment was functionally localized to the area of the left prefrontal cortex with the greatest functional anti-correlations to the subgenual cingulate cortex (SCC). Measures of functional connectivity were calculated before and after treatment and related to clinical response, as measured by the Hamilton Depression Rating Scale (HAMD-17). Relationships were tested for significance between the SCC, the target of stimulation, and 7 predefined networks representative of brain function. All inferences were corrected for multiple comparisons using permutation tests (for network comparisons) and considered significant for $p < .05$.

Results: Of the 17 subjects, 8 responded after completing TMS, and 7 remitted. There was significant anatomical overlap between the sites of stimulation of the responders and non-responders, with the peak of stimulation near Broadmann Area 46 for both groups. The course of TMS was not shown to alter the functional connectivity between the target of stimulation and

the SCC (p = 0.83, two-tailed), as measured through resting state fMRI. Still though, changes in connectivity (post – pre), as seen in **Fig. 1**, between the target of stimulation and the SCC, were significant predictors of antidepressant response (p = 0.014, two-tailed). Beyond the site of stimulation, baseline functional connectivity between the SCC and default mode network (DMN) predicted the magnitude of antidepressant response (p = 0.018, two-tailed), and changes in connectivity between the SCC and DMN observed after TMS also predict the magnitude of antidepressant response (p = 0.024 one-tailed).
Conclusion: Although it is known that TMS can make long term changes to brain activity, our results do not show TMS induced changes in functional connectivity. Despite the lack of group connectivity changes observed, our results do show that both baseline and changes in levels of functional connectivity can be predictive of antidepressant response. As may be expected based on previous research exploring the functional basis of depression, the default mode network, a system involved in self-inspection and rumination, was shown to be strongly related to antidepressant response. Interestingly though, our results show that increases in connectivity between the SCC and the DMN are related to antidepressant response, which is contrary to what has been previously reported. Our predictors analyses further show that individuals with weaker baseline connectivity also see the greatest antidepressant response, suggesting that it is important for patients with depression to achieve strong connectivity between the SCC and the DMN, and that individuals with already high baseline connectivity may have less to gain from TMS.

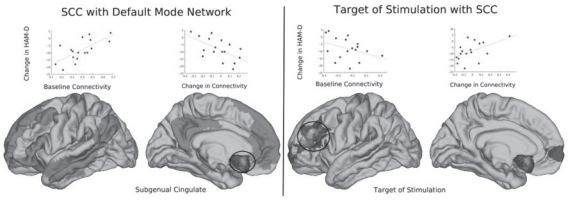

Figure 1: Comparing baseline connectivity and changes in functional connectivity to antidepressant response. In both the left and right panel, changes in HAM-D 17 scores (post – pre) were related to baseline connectivity in the left plot, and changes in HAMD-D 17 (post –pre) scores were related to changes in connectivity (post – pre) in the right plot. The left panel highlights functional connectivity between the SCC and DMN, and the right panel highlights functional connectivity between the SCC and target of stimulation.

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Guinevere Q. Lee, PhD, Ragon Institute

HIV reservoir establishment during hyperacute clade C infection

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Introduction: Little is known about the establishment of HIV reservoir at the earliest stage of infection. Here, we analyzed HIV-1 reservoir seeding in women with hyperacute infections identified in Durban, South Africa through weekly screening of high-risk individuals.
Methods: We analyzed proviral and plasma HIV-1 RNA from four individuals (patients code: treated F1,F2; untreated F3,F4). Total DNA was extracted, diluted for single-template full-HIV-genome PCR, and Illumina deep-sequenced. Sequences were classified into "genome-intact" or "defective," defined as the absence/presence of deleterious insertions/deletions/premature stop codons. Tropism was inferred by geno2pheno[coreceptor] at 20% FPR cutoff. Plasma RNA was subjected to full-genome-sequencing using Illumina or Pacific Biosciences platform.
Results: PBMC were collected on day 10, 2, 7, 18 after first positive HIV-1 RNA assays, corresponding to day 52, 5, 10, 40 after most-recent negative HIV-1 RNA assays; additional samples were collected at 3, 6, and 12-month. Among 287 full-genome-HIV vDNA detected, 87 were genome-intact (F1 6/53, F2 13/19, F3 8/27, F4 60/188). Genome defects included 5'deletion(9/287), APOBEC3G/3F-mediated hypermutations(22/287), premature stop codons in *gag/pol/env*(12/287) and large deletions(157/287). Compared to chronic infections, reservoir size was low at 3.4, 2.2, 0.8, 31.1 genome-intact-HIV per million PBMC at the most acute timepoint and decreased over time, whereas proportions of genome-intact HIV at the most acute timepoint were 14%, 82%, 100% and 35%, higher than previously described in chronic infections. Intrahost genetic distances were extremely small over time; majority were single-base substitutions distributed evenly across-genome: min/max pairwise differences were 2-4bp (F1), 1-7bp (F2), 4-18bp (F3) and 0-66bp (F4). Mutations accumulated over time in the two viremic patients: pairwise differences increased from median 7.5 to 18bp (F3; day 42-164) and 4 to 39bp (F4; day 18-332). No change in tropism was observed over time: R5 (F1), non-R5 (F2), non-R5 (F3), R5 (F4). In F4, complete identity between plasma virus and proviral HIV-1 DNA was observed.

Conclusion: These data are consistent with establishment of small proviral reservoirs with high levels of sequence homogeneity. We show a limited sequence diversification of proviral DNA over one year post-infection; single-base substitution mutations were the major source of viral diversity.

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Sara R. Lehrhoff, Masters of Science, Performance Analysis and Improvement/Practice Improvement

The impact of workplace engagement on physicians with high and low levels of burnout

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Introduction: Numerous studies have demonstrated the negative impact of burnout on physician turnover, patient safety, and quality of care.[1, 2, 3] Recent publications using national survey data show increasing levels of burnout and discontent among physicians leading to widespread discussion about the wellbeing of physicians.[4] In the field of organizational behavior, the concept of "work engagement" – a positive work-related state of fulfillment has been introduced as a positive representation of the psychologic state related to work. The Utrecht Work Engagement Scale is a 9-item instrument that measures work engagement using questions in each of three areas – vigor, dedication, and absorption.[5] Work engagement has been described as the "opposite" of burnout. Indeed, several studies have shown a strong inverse correlation between the two instruments. However, to date there are no published studies of work engagement among physicians using this tool and no studies examining the relationship between burnout and engagement among physicians. In this study, we aim to describe the impact of workplace engagement on physicians with high and low levels of burnout. In addition, we identify drivers of workplace engagement in these two groups of physicians.

Methods: We used data from the 2014 Massachusetts General Physician Organization (MGPO) survey to study the drivers and impact of engagement among academic physicians. To get a better understanding of the drivers and impact of engagement, we first divided the sample into those who showed high levels of burnout and those who did not. We then used logistic regression to identify drivers of engagement and assess the impact of engagement on career satisfaction and reported likelihood of staying in one's current job. Burnout was assessed using the Maslach Burnout Inventory-General Service (MBI-GS),[6] and physicians who scored high on at least two of the three subscales were defined as having high levels of burnout. Similarly, work engagement was assessed using the Utrecht Engagement Scale (UWES) and physicians who scored high on two of the three scales of engagement were defined as engaged. Career satisfaction was assessed using a five-point Likert Scale question, and physicians who responded with very satisfied or satisfied were defined as satisfied with their career. Finally, likelihood of staying at current job (retention) was assessed using a proxy question that asked physicians about their plan for the next three years. Physicians who responded with 'continue as I am' for this question were defined as 'staying'.

Results: Of the 1774 physicians who completed the survey, 720 (40.6%) showed high levels of burnout and 1054 (59.4%) showed mild or no signs of burnout. Predictably, work engagement was lower among those who had high levels of burnout than those who did not (35.8% vs 82.5%). In a multivariate logistic regression model predicting engagement, we found the factors that drive engagement may vary depending on the degree of burnout. For physicians with high levels of burnout, having an opportunity to consult with peers, satisfaction with workload, and having a trusted advisor increased likelihood of engagement. For physicians with mild or no signs of burnout, satisfaction with workload and opportunity to consult with peers were not significant drivers of engagement, but having a trusted advisor was. In both samples, we found engagement was associated with higher levels of career satisfaction and higher likelihood of staying. In a multivariate logistic regression controlling for age, gender, race, and specialty, we found the impact of engagement on likelihood of staying does not depend on the degree of burnout (OR 1.81, 95% CI=1.3 – 2.5 for physicians with high levels of burnout vs OR=1.80, 95%CI=1.26 -2.6 for physicians without high levels of burnout), but the impact of engagement on career satisfaction was higher among physicians with high levels of burnout (OR=7.14, 95% CI=4.1 – 12.5 for physicians with high levels of burnout vs OR=4.4, 95%CI=2.2 – 8.5 for physicians without high levels of burnout).

Conclusion: We found that among physicians with and without high levels of burnout, work engagement, including vigor, dedication, and absorption, was associated with higher career satisfaction and higher reported levels of staying in one's current role. These findings suggest that among physicians, work engagement may not be an exact antipode to burnout, but rather a different dimension of one's relationship to work that has some protective benefit. In our multivariate regression model, among both cohorts, physicians who reported having a trusted advisor were showed higher levels of engagement; and among physicians who had high levels of burnout, the ability to consult with peers increased engagement. Together, these findings suggest the importance of relationships between physicians, both peer and advisory, to the wellbeing of academic physicians. Our study suggests that as AMCs face scarce resources and an emerging epidemic of burnout, emphasizing connectivity among faculty is a critical aspect of addressing this crisis.

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Jacob Lemieux, MD, DPhil, Medicine - Infectious Diseases

Human and Microbial Genetic Factors Important in Tick-Borne Disease

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Introduction: Infections transmitted by the deer tick, *Ixodes scapularis,* are an increasingly important cause of disease in the United States, particularly in the Northeast. Lyme disease, babesiosis, anaplasmosis, and the more recently-recognized *Borrelia miyamotoi* and Powassan Virus, are rising in incidence and expanding their geographic range. These infections present with a wide spectrum of clinical illness that is poorly understood. For example, patients with Lyme disease experience symptoms ranging from skin rash to meningitis; individuals with Babesiosis present along a spectrum of mild febrile illness to hemolytic anemia, septic shock and sometimes death. We hypothesize that host and microbial genetic factors underlie the heterogeneity of clinical disease and propose to identify genes that contribute to disease-specific clinical manifestations of tick-borne illness.

Methods: Subjects with known or suspected tick borne disease and control individuals are enrolled at four Partners sites: Massachusetts General Hospital, Brigham and Women's Hospital, Newton Wellesley Hospital, and Nantucket Cottage Hospital. Physicians at participating sites identify potential patients by paging the Partners-wide "tick" pager (26763 or "tick" in the Partners Paging Directory) based on known or suspected tick borne disease manifestations or exposure. Study staff obtain consent from eligible and interested patients. We collect clinical and exposure data, isolate host and microbial specimens, and perform genotyping by whole genome sequencing. Data and samples are stored in a secure sample bank and research repository.

Results: We have enrolled 116 patients, including 41 with Lyme disease, 35 with babesiosis, 15 with anaplasmosis, 2 with *Borrelia miyamotoi*, and 3 with powassan virus (Table 1). We have developed a target capture method for these pathogens using hybrid selection, facilitating whole genome sequencing from low-input material. Initial efforts have focused on human babesiosis infection. We have sequenced 42 *B. microti* genomes from individuals with uncomplicated and relapsing babesiosis. Relapsing cases of babesiosis contain an excess of protein-coding polymorphisms in parasite-encoded cytochrome B and RPL4, the known targets of atovaquone and azithromycin resistance, respectively. These variants occur in drug binding regions of these proteins and resemble atovaquone and azithromycin resistance mutations in related parasites, including *Plasmodium falciparum*.

Conclusion: We have established a clinical infrastructure to study host and microbial genetic determinants of tick borne disease in New England. Whole genome sequencing of *B. microti* from patients with babesiosis identifies genetic variants associated with relapsing babesiosis, likely through evolution of parasite drug resistance. This is one of the first examples of a microbial genetic factor influencing the spectrum and severity of a tick-borne disease and demonstrates the efficacy of this approach.

	Clinical Diagnosis					
Cohort Demographics	All Subjects N = 116	Babesiosis N = 35	Lyme Disease N = 41	Anaplasmosis N = 15	Other* N = 11	Control N = 31
Mean Age at Enrollment (± STD, yrs)	58.5 ± 16.6	66.8 ± 13.1	58.1 ± 17.2	63.6 ± 12.0	56.0 ± 17.1	53.1 ± 16.0
18-30, n (%)	11 (9.5%)	0 (0%)	5 (12.2%)	0 (0%)	1 (9.1%)	5 (16.1%)
31-50, n (%)	22 (19.0%)	6 (17.1%)	7 (17.1%)	2 (13.3%)	4 (36.4%)	5 (16.1%)
51-70, n (%)	55 (47.4%)	14 (40.0%)	17 (41.5%)	9 (60.0%)	4 (36.4%)	18 (58.1%)
71-90, n (%)	28 (24.1%)	15 (42.8%)	12 (29.3%)	4 (26.7%)	2 (18.2%)	3 (9.7%)
>91, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Male, n (%)	76 (65.5%)	28 (80%)	30 (73.2%)	10 (66.7%)	6 (45.5%)	18 (58.1%)
Ethnic Group (known, %)	113 (97.4%)	32 (91.4%)	40 (97.6%)	15 (100%)	11 (100%)	31 (100%)
African American / Black, n (%)	3 (2.6%)	1 (2.9%)	1 (2.4%)	0 (0%)	1 (9.1%)	0 (0%)
Asian, n (%)	5 (4.3%)	4 (11.4%)	2 (4.9%)	0 (0%)	0 (0%)	1 (3.2%)
White, n (%)	101 (87.1%)	25 (71.4%)	37 (90.2%)	15 (100%)	10 (90.9%)	29 (93.5%)
Other, n (%)	4 (3.4%)	2 (5.7%)	0 (0%)	0 (0%)	0 (0%)	1 (3.2%)
Hispanic, n (%)	4 (3.4%)	1 (2.9%)	2 (4.9%)	0 (0%)	1 (9.1%)	1 (3.2%)

*POWV; *B. miyamotoi*; Tularemia; Malaria; Chronic Lyme

Table 1: Patient Demographics

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Umme Lena, Bachelors of Arts, Center for Human Genetic Research (CHGR)

Association of brain atrophy and leukoaraiosis with intracerebral hemorrhagic characteristics and their impact on mortality

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Introduction: Intracerebral hemorrhage (ICH) volume and presence of intraventricular hemorrhage (IVH) are known predictors of ICH outcome. Because cerebral small vessels disease (SVD) risk factors influence risk of ICH, we aim to investigate the relationship between two SVD neuroimaging biomarkers, atrophy and leukoaraiosis, and: 1) ICH volume and IVH presence; 2) ICH mortality.

Methods: Data was derived from Ethnic/ Racial Variation of Intracerebral Hemorrhage (ERICH), a prospective, multi-center, study of primary ICH patients. Subjects' leukoaraiosis and atrophy were assessed on admission CT respectively with the van Swieten scale (ranging from 0 to 4), and global atrophy (none, moderate, or severe). We also measured: IVH presence, ICH volume (on the same CT), and 90-day mortality. Other clinical covariates included past medical history, medications, ICH location and pre-ICH modified Rankin scale (mRS) were collected. Multi-adjusted regression analyses were used to examine association between atrophy and leukoaraiosis and IVH and ICH volume, as well as, 90-day mortality.

Results: Of 1009 patients, available, 139 were excluded due to poor CT quality. Included patients (62.2% male; median age 60 (Inter Quartile Range [IQR] 52-73)) had a mean ICH volume of 16.7 (SD [standard deviation] ±20.5), van Swieten of 1.4 (SD±1.5), and mean atrophy of 1.6 (SD±1.4); 313 (36.1%) presented with IVH. After adjusting for confounders, severe atrophy was associated with higher risk of IVH (Odds Ratio [OR] 1.29, 95% Confidence Interval [CI] (1.11-1.49), p= 0.001), but with lower ICH volume (β=-0.12, 95% CI (-0.13- -0.03), p= 0.02). Severe leukoaraiosis was associated with lower ICH volume (β=-0.08, 95% CI (-0.09- -0.01), p= 0.021), but not with IVH (OR 0.90, 95% CI (0.80-1.01), p= 0.067). 90-day mortality rate was 9.8%. When estimating the effect of both biomarkers on mortality, severe leukoaraiosis, and not atrophy, was a significant predictor of mortality (OR 1.23, 95% CI (1.07-1.41), p= 0.004).

Conclusion: Leukoaraiosis is associated with reduced ICH volume, but remains a predictor of ICH mortality. In contrast, atrophy does not impact mortality after ICH, possibly due to its concurrent role as a determinant of both IVH presence and decreased ICH volume. These results highlight the complex relationship between radiographic markers of SVD and clinical outcomes after ICH. More work will be needed to explore the independent effects of these and other SVD markers on ICH outcome.

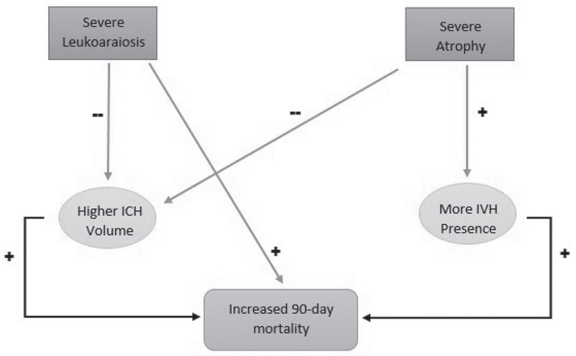

Figure 1. Significant findings of the relationship between SVD neuroimaging biomarkers and ICH characters and outcome.

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Michael J. Leone, Neurology

Rapid Detection of Infectious Disease Pathogens and Autoimmune Antibodies in Encephalitis

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Introduction: Rapid and accurate diagnosis of central nervous system infection is a major unmet need in clinical neurology and infectious diseases. Started in 2016, the Prospective Encephalitis and Meningitis Study (PEMS) is led by a multidisciplinary team of clinician-researchers in neurology, infectious diseases, immunology and pathogen genomics at MGH and the Broad Institute. The PEMS objective is to develop diagnostic workflows that integrate emerging technology including metagenomic sequencing and high-throughput proteomic assays for pathogen and autoantibody detection with extensive clinical phenotyping. Here, we present patient characteristics and study design to date.

Methods: PEMS is an observational cohort of MGH patients with suspected encephalitis and meningitis. Inpatients are recruited by referral from clinicians; outpatients are recruited in the MGH Neurology Lumbar Puncture (LP) clinic if suspected of chronic infection or antibody-mediated autoimmune encephalitis. Detailed clinical information is collected in a secure Research Electronic Data Capture (REDCap) database, including hospital-related conditions, co-morbidities, medications, infectious disease exposure risks, and daily imaging, EEG data and labs. Stored biofluids include excess or additional tubes of cerebrospinal fluid (CSF), blood, urine, and when available, excess brain biopsy tissue. The study is approved by the MGH Institutional Review Board and informed consent was obtained from all participants.

Results: Clinical characteristics of the first seventy five patients enrolled are shown in Table 1. The average age is 55 years (SD: 16.6), irrespective of inpatient or outpatient status. Sixty two (83%) individuals identify as non-Hispanic White, and 6 (8%) individuals identify as Black or African American. Inpatients make up 80% of the cohort; 20% are HIV-1 infected. While the majority of inpatients presented with symptoms concerning for infectious meningitis or encephalitis (77%), final diagnoses were notably heterogeneous (Figure 1). Ten (16%) inpatients had viral infections identified by CSF polymerase chain reaction (PCR), while 24 (39%) inpatients were identified with infectious/para-infectious encephalitis by serology. Thus far, the study has enrolled 11 inpatients with a diagnosis of autoimmune/non-infectious etiology. Final diagnosis remains unknown in 17 (27%) cases. To efficiently capture medical record data, the PEMS team developed a Python program for automatic Research Patient Data Registry (RPDR)-to-REDCap import. The software imports structured demographic information, daily ICD-10 codes, medications including dosage and frequency, allergens, and results for 108 classes of lab tests from CSF, blood, and urine. Automatic import saves personnel two hours per patient per day, reduces human error and represents over 25,000 entries for the cohort. Semi-structured (eg. send-out tests) and unstructured (eg. imaging interpretations) data are filled manually based on EPIC chart review. PEMS currently houses CSF (n=67), blood (n=7), and urine (n=2) samples. Metagenomic sequencing for infectious pathogen discovery has been performed for 42 patients (see poster: "*Unbiased pathogen detection in patients with central nervous system infection using metagenomic sequencing*"). Proteomic analysis in CSF and serum for antibody-mediated encephalitis is ongoing (n=22).

Conclusion: In the last 12 months, the interdisciplinary PEMS team has optimized automated entry of structured data, saving time and reducing human error, and has successfully incorporated metagenomic sequencing of CSF and other biofluids into its diagnostic workflow. Long-term goals are to provide relevant diagnostic information to patients with encephalitis and their physicians within a clinically meaningful timeframe, and to predict outcomes based on the medical record using methods in applied statistics and machine learning.

Table 1. PEMS: Patient Demographic and Clinical Data

	Total Cohort	Inpatient	Outpatient
No. Subjects	75	62	13
Age in years, mean (sd)	55 (16.6)	55 (17.5)	55 (11.6)
Male, n (%)	50 (67%)	40 (65%)	10 (77%)
Non-Hispanic White, n (%)	58 (83%)	49 (86%)	9 (69%)
HIV+, n(%)	15 (20%)	6 (10%)	9 (69%)
MRI performed within month of admission/visit, n (%)	54 (72%)	46 (74%)	8 (62%)
Abnormal MRI (%)	46 (85%)	40 (87%)	6 (75%)
Elevated CSF WBC Count, n (%);	43 (60%)	43 (72%)	0 (0%)
Elevated WBCs, median [range]*	45 [6,4175]	45 [6,4175]	NA
Lymphocyte Predominant, n (%)*	32 (74%)	32 (74%)	NA
Abnormal Glucose, n (%);	31 (43%)	29 (48%)	2 (17%)
Abnormal Protein, n (%);	38 (53%)	36 (60%)	2 (17%)
Fever, n (%)		32 (52%)	
Headache, n (%)		32 (52%)	
Photophobia, n (%)		17 (27%)	
Altered Mental Status, n (%)		37 (60%)	
Confirmed or suspected seizures, n (%)		16 (26%)	
Suspected Meningitis or Encephalitis, n (%)		48 (77%)	
Survival at Discharge, n (%)		59 (95%)	
Length of Hospital Stay, median [range]		14 [2,51]	

Note: Percentages calculated from reported values.

*calculated among CSF profiles with elevated WBC count (>5 cells/ul)

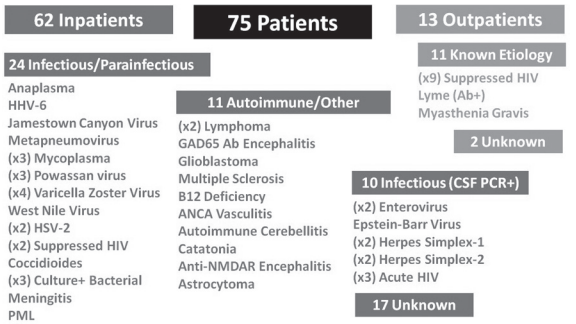

Figure 1: Study participant diagnoses. Of 13 outpatients, 11 were diagnosed (Known Etiology); 2 are undiagnosed (Unknown). Of 62 inpatients, 10 were diagnosed by PCR; 24 were diagnosed with infection/para-infection by serology; 11 with autoimmune or non-infectious disease; in 17 cases, the diagnosis is unknown.

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Katherine A. Levandoski, BS, Dermatology

Comparative effectiveness of treatment of actinic keratosis with topical fluorouracil and imiquimod

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Introduction: Actinic keratoses (AKs) are precancerous skin lesions that are prevalent and costly, accounting for >$1 billion in healthcare expenditures annually in the United States. The two most widely used topical agents for the field-based treatment of multiple AKs are 5-fluorouracil (5-FU) and imiquimod. Although small clinical trials have examined the efficacy of both agents for AK treatment, no prior studies, to our knowledge, have compared the real-world effectiveness of 5-FU and imiquimod for preventing subsequent AKs. The objective of this study was to compare the effectiveness of 5-FU and imiquimod in reducing risk of subsequent AKs in a community-based setting.

Methods: We conducted a retrospective cohort study at Kaiser Permanente Northern California (KPNC), a large, integrated healthcare delivery system. We identified all adult KPNC health plan members that had an AK diagnosed between January 1, 2007 and December 31, 2007 and who received subsequent topical field-based treatment with 5-FU or imiquimod (n=5,700) (Figure 1). Subjects were excluded if 5-FU or imiquimod was prescribed for any indication other than AK, or if they had a history of ultraviolet light treatment or immunosuppression. Exposure was defined as pharmacy dispensing of either 5-FU or imiquimod following an AK diagnosis in 2007. The main outcome was time to subsequent AK diagnosis after cohort entry. Subjects were followed starting at treatment dispensing and until the earliest of death, health plan disenrollment, a subsequent AK diagnosis, or the end of the study period on December 31, 2012. A propensity score approach controlling for potential confounding by pre-treatment variables was used to estimate the 2-year ("short-term") and 5-year ("long-term") differences in cumulative risk for subsequent AKs between the two groups of patients treated with 5-FU and imiquimod.

Results: Among cohort members, 5,062 were exposed to 5-FU and 638 were exposed to imiquimod. The majority (n=4,946) were diagnosed with a subsequent AK during follow-up. 5-FU reduced the short-term incidence of subsequent AK (adjusted cumulative risk difference -4.54% [95% confidence interval (CI): -7.91% to -1.17%]), but there was no statistically significant evidence of a long-term decreased risk of subsequent AK (adjusted cumulative risk difference -1.43% [95% CI: -3.43% to 0.05%]) compared to imiquimod (Figure 2).

Conclusion: Within a real-world practice setting of an integrated healthcare delivery system, we found that 5-FU was significantly more effective than imiquimod in preventing subsequent AKs in the short-term, but not the long-term. These results can potentially inform patients and clinicians in selecting field-based treatments for multiple AKs.

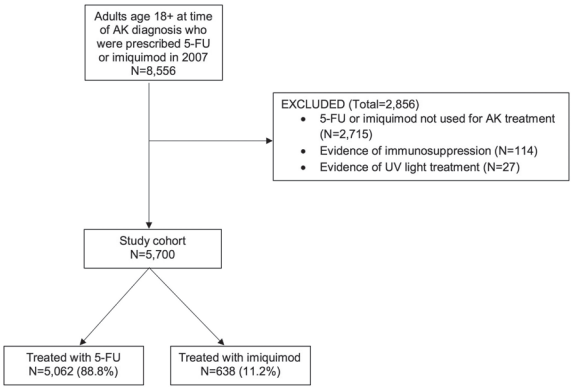

Figure 1. Study Flow Diagram. Flow diagram depicting the derivation of the study cohort.

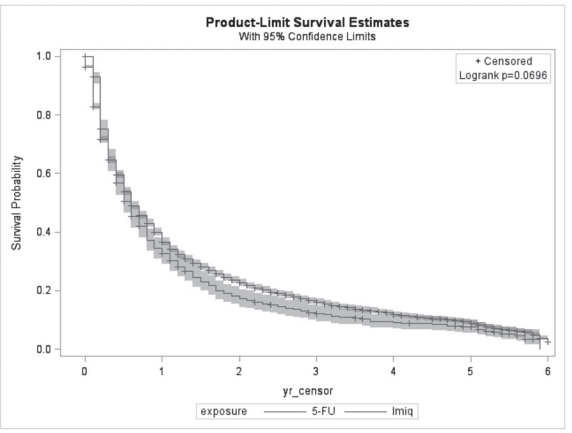

Figure 2. Kaplan-Meier Estimators. Kaplan-Meier estimators showing the probability of subsequent actinic keratosis (AK) based on treatment type. The Kaplan-Meier estimators indicate a statistically significant reduction in risk of subsequent AK for 5-FU compared to imiquimod at 2 years but not at 5 years.

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Nina Levar, Psychiatry

Impairments in resting state activity are associated with cannabis use and major depressive disorder

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Introduction: Cannabis use has been associated with abnormalities in brain activity and brain structure, as well as cognitive deficits. Despite anecdotal reports of its benefits, little is known about how cannabis use impacts the brain among patients with Major Depressive Disorder (MDD). This study examined differences between cannabis users and non-users with and without MDD in activity in the three core networks implicated in psychopathology the default-mode network (DMN), the salience network (SN), and the central executive network (CEN).

Methods: Eighty-one participants between the ages 18-25 years completed a neuroimaging study. Nineteen cannabis users without MDD (MJ), 19 marijuana users with current and/or past MDD (MDD-MJ), 24 non-using controls without MDD (CON), and 19 non-users with current and/or past MDD (MDD) were enrolled. MRI scans were acquired at the Martinos Center for Biomedical Imaging. A high resolution structural T1 scan and a resting-state scan were acquired. Participants completed a timeline follow-back interview assessing cannabis and alcohol use over the past 90 days. Depressive and anxiety symptoms were assessed using the Mood and Anxiety Symptom Questionnaire. Resting state networks were extracted using independent component analysis (ICA) in Melodic in FSL. Components representing the DMN, SN, and the left and right CEN were identified based on standard network definitions. Permutation tests were used to assess differences in network activity between groups for the four networks ($p<0.05$). Partial correlations between networks were calculated for HC, MJ, MDD, and MDD-MJ groups separately. Correlation coefficients for pairwise network correlations were extracted and correlated with demographic and clinical measures across groups.

Results: Five ICA components were selected for the anterior DMN (aDMN), posterior DMN (pDMN), SN, and the left and right CEN. MDD had increased resting state activity than CON, MJ, and MDD-MJ in the aDMN (e.g. frontal pole, ACC, frontal medial cortex), the salience network (e.g. insula, caudate, putamen), and left and right CEN (e.g. precuneus, lateral occipital cortex, superior parietal lobe). MDD also showed greater activity compared to CON and MJ in the pDMN (e.g. posterior cingulate gyrus, angular gyrus). MDD-MJ had increased activation in the pDMN compared to MJ.

Conclusion: Results show that cannabis use and symptoms of major depressive disorder are associated with differences in resting state activity in the DMN, SN, and CEN, with depression having the largest effect across networks. Cannabis use is associated with increased activity compared to non-using controls, while depressed cannabis users show reduced activation compared to MDD in all networks except the pDMN. Even though cannabis use was associated with a reduction in resting state activity in depressed individuals, future work is needed to examine whether connectivity between networks is linked with differences functional outcomes including MDD symptoms and cognitive functioning. It is possible that cannabis use reduces aberrant resting state activity associated with MDD, but might disrupt the interplay between networks, thereby impairing cognitive processes such as episodic memory and attention.

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Julie Levison, MD, MPhil, MPH, FACP, Medicine - General Internal Medicine

HIV Testing Outcomes in a Multi-National Cohort of Latino Migrants with Substance Use and Mental Health Problems

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Introduction: Individuals with substance use disorders and migrants are at high risk for undiagnosed HIV and are key populations to achieve the United Nation's 90-90-90 targets.
Methods: We used HIV and sexually transmitted infection (STI) biomarkers from a multi-national randomized trial of a behavioral intervention for Latino migrants. Eligibility criteria were: age 18-70 years; positive screen for substance use and mental health problems; and not enrolled in substance or mental health care. Risk behaviors and clinical history were assessed at baseline. HIV and STI testing was offered at week-6 using rapid HIV testing (OraQuick, OraSure Technologies, Inc) and urine nucleic acid amplification for *Chlamydia trachomatis* and *Neisseria gonorrhea.* A multinomial logistic regression examined potential predictors of HIV or STI test decline or loss to follow-up (LTFU) compared with acceptance.
Results: Of the 341 participants, 252 (74%) accepted HIV/STI testing, 15 (4%) refused, and 74 (22%) were LTFU. Lifetime injection drug use was low (3%) and 16% (n=53) reported condomless anal sex. The multivariate model suggests a lower odd of test refusal when participants were recruited at a community agency or by personal referral compared with primary care site (OR=0.66 [95% CI 0.44-1.00]), and when the main partner had undergone HIV testing (OR=0.32 [95% CI 0.14-0.75]). LTFU prior to testing was lower in those with a college degree or higher (OR 0.14 [95% CI 0.13-0.15]) and higher in those who reported a high concern for HIV compared with no concern (OR=1.49 [95% CI 1.14-1.96].
Conclusion: Nearly three-quarters of Latino migrants accepted HIV/STI testing. Those most concerned for HIV and with lowest education were more likely to drop out prior to test offer. Mechanisms to personalize the delivery of testing, such as community-based delivery or referral by a known person, may help overcome these barriers to HIV/STI services in this population.

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Edward Li, BA, Center for Regenerative Medicine (CRM)

Rapid Functional Analysis of Computationally Complex Rare Human *IRF6* Gene Variants Using a Novel Zebrafish Model: Personalized Medicine in Cleft Lip and Palate

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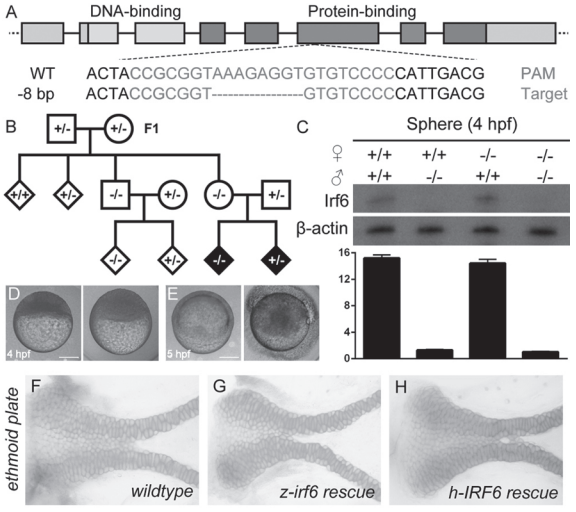
Introduction: Cleft lip and/or palates (CL/P) are among the most common congenital malformations. Mutations in the transcription factor gene *IRF6* represent the most significant genetic contributors to orofacial clefts. Hundreds of novel sequence variations in *IRF6* have been reported. However, the functional significances of the myriad of *IRF6* mutations remain difficult to ascertain as in silico prediction programs have poor predictive power and often provide conflicting results. To address this gap in knowledge, we hypothesized that the protein function of *IRF6* gene variants could be rapidly assessed by their ability to rescue the *irf6-/-* mutant phenotype in animal models.
Methods: CRISPR genome editing was used to generate *irf6-/-* zebrafish. Previously uncharacterized *IRF6* variants were identified and categorized by computational predictions from Polyphen2 and SIFT. Variants were introduced to wildtype *irf6* cDNA by site-directed mutagenesis; mRNA was produced by in vitro transcription and microinjected into *irf6-/-* embryos to assess for phenotypic and functional rescue.
Results: All offspring of *irf6-/-* females displayed an embryonic rupture phenotype caused by defects in the embryonic periderm, a simple squamous epithelium surrounding the embryo that models the human oral epithelium. The periderm rupture model is validated for use in the analysis of human *IRF6* function, as injection of human *IRF6* mRNA into mutant zebrafish embryos can fully rescue the mutant phenotype. Human *IRF6* gene variant mRNAs were then injected in a rapid and accurate rescue assay to assess the effects of human *IRF6* mutations on protein function. The *IRF6* gene variant rescue results revealed that neither location of the mutations within the IRF6 protein nor computational programs were accurate predictors of whether observed human *IRF6* mutations actually resulted in defective proteins. Several variants predicted to be benign failed to rescue, while others predicted to be deleterious by both computational programs were able to rescue not only periderm rupture, but also normal craniofacial development.

Conclusion: The zebrafish *irf6-/-* rescue assay rapidly addressed the functional significance of novel *IRF6* mutations and overcame computational limitations for predicting variant pathogenicity. These validated biological results can help improve future computational predictions, and moreover, unlock the possibility for rapidly characterizing yet undiscovered *IRF6* variants from orofacial cleft patients, illustrating a generalizable functional genomics paradigm of personalized medicine.



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	Computational Deleterious		Computational Disagreement	
	Mutation	Result	Mutation	Result
N-linker	R9W	Rescued	R6C	Rescued
DNA-binding	W60G	Ruptured	P74L	Rescued
Mid-linker	P222L	Rescued	P197S	Rescued
Protein-binding	L294P	Ruptured	R250Q	Ruptured
C-linker	I423T	Rescued	R400Q	Rescued

Figure 1: Characterization of the zebrafish *irf6* mutant model and testing human *IRF6* gene variants. (A) CRISPR gene editing generated a -8bp indel mutation resulting in a premature stop codon.(B) Breeding pedigree.(C) qPCR and western blot reveal a lack of *irf6* mRNA/protein in mutant embryos.(D-E) Periderm rupture phenotype.(F-H) Rescue of palate development in zebrafish and human *IRF6* mRNA-injected mutants compared to wildtype.(I) Results of the variant mRNA rescue experiments categorized by mutation location within the IRF6 protein and computational predictions.

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Hua Li, M.D., Radiology

Precision Imaging Metrics: All-in-one Quantitative Imaging Assessment and Workflow Management System for Oncology Clinical Trials

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Introduction: Oncology clinical trials have become increasingly dependent upon image-based surrogate endpoints for determining patient eligibility and treatment efficacy. As therapeutics have evolved and multiplied in number, the tumor metrics criteria used to characterize therapeutic response have become progressively more varied and complex. The growing intricacies of image-based response evaluation, together with rising expectations for rapid and consistent results reporting, make it difficult for site radiologists to adequately address local and multicenter imaging demands. These challenges demonstrate the need for advanced cancer imaging informatics tools that can help ensure protocol-compliant image evaluation while simultaneously promoting reviewer efficiency.

Methods: The Tumor Imaging Metrics Core (TIMC) was established in 2004 to address the Dana-Farber/Harvard Cancer Center needs by providing centralized imaging review services for patients enrolled in oncologic clinical trials. We developed and implemented an informatics infrastructure, branded Precision Imaging Metrics to promote communication between oncology and radiology teams, and enhance review and reporting processes, timeliness, and quality,. The Precision system provides cancer centers with a clinical trial informatics platform tailored to the specific workflow needs of site review. Architecturally, the platform consists of two interconnected software applications: a proprietary web-based workflow management

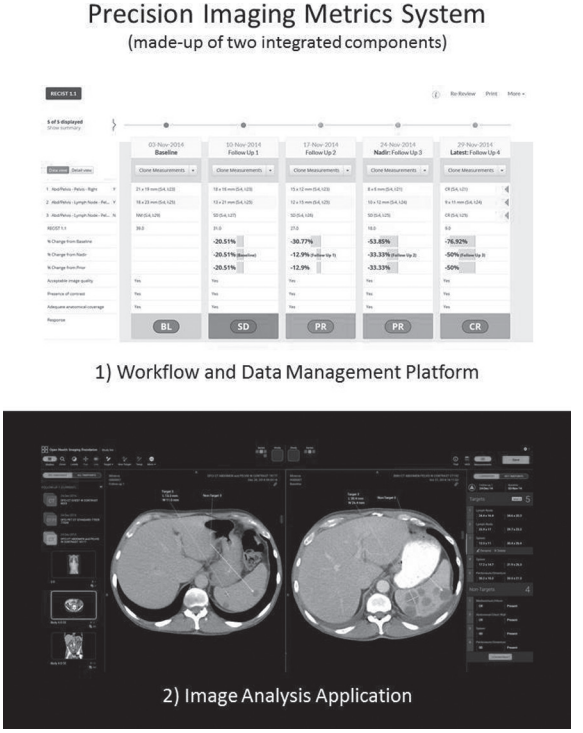
system and an open-source image analysis tool known as LesionTracker, which will replace the currently deployed desktop imaging application (Figure 1). LesionTracker is available under an open source, commercially permissive software license (MIT) and is designed with a modular architecture that enables it to be easily extended and integrated with third-party informatics applications. The shift to a web-based system for image assessments rather than a workstation-based installed application will improve workflow efficiency, enhance accessibility, and promote collaborative image review for the radiologists and clinical providers at cooperating cancer centers.

Results: The Precision Imaging Metrics solution eliminates paper measurement forms and other outdated, error-prone tools and practices. The local clinical treatment team can request scan analyses, specify the time when results are needed, and view imaging results through a secure, password-protected website. Built-in response criteria conformance checks ensure that the imaging reviewers assess the scans according to the trial-specific protocol and response criteria. Upon saving image measurements, quantitative metrics and annotated images are automatically uploaded to the website. After electronic sign-off by the reviewing radiologist, the imaging time point is locked and the clinical team is automatically alerted that the assessment is ready for viewing. Results are provided on-line and on-time, before the patient is seen in the clinic for treatment decisions. The clinical team can access measurement tables, graphs, and annotated images in a single structured report and can print a copy of the report to serve as the source document for trial audits. The Precision Imaging Metrics system is available through an academic licensing model and is currently in use at seven NCI-Designated Cancer Centers across the country as a NCI-shared resource (Table 1). The fully web-based system will be available for deployment at sites in early 2018.

Conclusion: Oncologic clinical trials are increasing in their complexity but most sites lack adequate image analysis solutions to meet the expectations of oncologists, radiologists, and trial sponsors. The Precision Imaging Metrics system has the potential to minimize inconsistencies throughout the image review and reporting process and promote timeliness as well as efficiency and collaboration across clinical teams and cancer centers.

Usage to Date of All Participating NCI-Designated Cancer Centers

Cancer Center	Location	Activation Date	Trials	Time Points
Dana-Farber / Harvard Cancer Center	Boston, MA	Aug. 2004	1,468	74,949
Yale Cancer Center	New Haven, CT	Sept. 2013	358	12,612
Fred Hutchinson Cancer Research Center	Seattle, WA	Sept. 2014	455	13,876
Huntsman Cancer Institute	Salt Lake City, UT	June 2015	72	1,568
Massey Cancer Center	Richmond, VA	Sept. 2015	54	463
Winship Cancer Institute	Atlanta, GA	Feb. 2017	127	409
Medical College of Wisconsin Cancer Center	Milwaukee, WI	Summer 2017	TBD	TBD



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Catherine Y. Liang, B.S., Medicine - Mongan Institute for Health Policy

Changes in Insurance Status and Continuity of Primary Care in the Post-ACA Individual Market

C.Y. Liang[1], V. Fung[1,2], S.J. Shah[3] and J. Hsu[1,4]

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Introduction: Increasing access to primary care was a key goal of the Affordable Care Act (ACA). Millions of Americans have gained insurance, potentially increasing access to medical care. However, concerns exist about the undersupply of primary care providers (PCPs), restricted provider networks in individual market plans, and limited consumer knowledge of provider networks, and their effect on enrollees' ability to obtain care. We examined how frequently individual market enrollees in California in 2014 had a regular PCP, and gains, losses or changes in their PCP from the prior year. We also assess variation by differences in enrollees' insurance status from 2013 to 2014.
Methods: We conducted telephone and web-based surveys among a random sample of 2,103 adult enrollees in California's individual insurance market in 2014. We asked whether they had a regular PCP in 2013 and a current PCP, reasons for changing PCPs, and changes in insurance status in 2013 to 2014. Insurance status was grouped into 3 categories: insured anytime in 2013 with the same plan as 2014, insured in 2013 with a different plan in 2014 (switched plans), and uninsured for all of 2013. We used multivariate logistic regression to assess the association between changes in insurance status and having a current PCP, stratified by whether enrollees had a PCP in 2013, adjusting for age, sex, race, language, education, income, and health status. We weighted all analyses by sampling proportions.
Results: Most enrollees (52%) were insured with different plans in 2013 and 2014, while 21% were insured with the same plan in both years and 27% were uninsured in 2013. Overall, the percent of enrollees with a PCP increased from 66% to 74% in 2013-2014 ($p< 0.05$): it increased from 34% to 71% among the previously uninsured vs. decreased from 79% to 76% among the previously insured. Among enrollees without a PCP in 2013, the percent who gained a PCP in 2014 varied by changes in insurance status between the two years: 61% of the previously uninsured, 44% of those insured with the same plan, and 38% of those who switched plans ($p< 0.05$). Among those with a 2013 PCP, the percent of enrollees who changed or lost their PCP also varied by insurance status changes: 41% and 10% of the previously uninsured, 23% and 11% of those with the same plan, and 29% and 16% of those who switched plans changed or lost PCPs, respectively. Among those who changed or lost PCPs, 55% reported it was because their prior PCP was not in their current plan network; of these enrollees, 59% were unaware of this at the time of plan selection. In multivariate analyses among enrollees without a 2013 PCP, compared to the previously uninsured, those who switched insurance plans were less likely to have a 2014 PCP (OR=0.57, 95% CI: 0.36-0.88).
Conclusion: The percentage of individual market plan enrollees in 2014 with a regular source of primary care increased from 2013. Plan switching, however, appears to be associated with disruptions in primary care, with network differences as a factor. Health insurance coverage expansion can improve access to primary care, but restricted provider networks coupled with limited consumer knowledge could hinder care continuity. Individual health insurance markets that encourage consumers to switch plans, e.g., in shopping for lower premiums, should consider downstream implications of plan changes.

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Alicia Lightbourne, MPH, Emergency

A ketamine-package to support emergency and essential surgery when no anesthetist is available: An analysis of 1,029 consecutive operations in Kenya

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Introduction: More than two-thirds of the world's population does not have access to emergency and essential surgery in a timely fashion. In many regions of Kenya and other resource-limited settings, access to life-saving surgeries is in a state of crisis. A major contributor to this unmet demand for surgery is the lack of anaesthesia services, with low- and middle-income countries, in particular, suffering a severe shortage of anaesthetists. To address this gap, the Every Second Matters for Emergency and Essential Surgery – Ketamine (ESM-Ketamine) package was designed and implemented. The first 1,029 consecutive operative procedures supported by the ESM-Ketamine package when no anesthetist was available were analyzed.

Methods: From December 2013 to April 2017, the ESM-Ketamine package was implemented for patients requiring emergency or life-improving surgeries in nine selected facilities across Kenya when no anaesthetist was available. Quantitative and qualitative methodologies assessed feasibility, safety, acceptability, and early insights into potential impact. Primary quantitative outcome measures included patient demographics, procedures, drug administration, and outcomes. Key-informant interviews captured perceptions of providers, hospital administrators, and surgeons/proceduralists.
Results: Non-anaesthetist mid-level providers used ESM-Ketamine for 1,029 surgical procedures across the nine study facilities. Mean total ketamine dose per case was 3.7 mg/kg. Brief (<30 seconds) desaturations occurred in 3.2% of cases, and hallucinations and agitation were treated with diazepam in 16.6%. There were six (0.6%) prolonged (>30 seconds) desaturation events, each with full recovery. Twenty-seven key-informant interviews showed strong support for the program with four main themes: financial considerations, provision of services, staff impact, and scaling.
Conclusion: The ESM-Ketamine package appears safe, capable of expanding access to emergency and essential surgeries, and is acceptable to community- based healthcare professionals in rural Kenya.

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David Lin, MD, Neurology

Investigation of the Neural Dynamics of Human Motor Learning Using an Intracortical Brain Computer Interface

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Introduction: The aim of this study is to use a human intracortical Brain Computer Interface (BCI) to investigate the neural dynamics of motor learning and motor system plasticity at the scale of single neurons and local field potentials. Recent studies employing brain computer interfaces in non-human primates have revealed fundamental insights into the neurophysiology of motor learning. The tuning properties of individual neurons evolve, and groups of neurons consolidate into stable networks. Studying the correlates of BCI learning in humans has traditionally been a more challenging task because to enable optimal BCI control of effectors, neural decoding algorithms need to adapt to non-stationary signals. Thus, real-world BCI decoders exhibit changing input features as well as model parameters making inferences about motor learning difficult to interpret.
Methods: Here we present a Local Field Potential (LFP)-based decoding paradigm that allows human participants enrolled in the BrainGate2 clinical trial to learn a relatively simple and arbitrary map between LFP power in the low-gamma range and one-dimensional cursor control. Specifically, the smoothed LFP power in the low-gamma range (40 – 55 Hz) from a single electrode selected from two 96-channel microelectrode arrays (Blackrock Microsystems, Salt Lake City, UT) placed in the dominant motor cortex was mapped based on threshold percentile values to constant speed leftward, resting, or rightward directional control of a cursor (paddle) during the game "Pong" presented on a computer screen.
Results: The decoder was successfully tested online with BrainGate2 clinical trial participant (T9), a 54 year-old man with amyotrophic lateral sclerosis. Our preliminary results indicate that T9 was able to improve directional control ability over the course of a single 30-minute session using this fixed decoder. We plan to analyze performance in additional participants over multiple days to assess for participant learning and subsequently analyze the evolving relationships between local field potentials and neuronal action potentials both on the control electrode and across both microelectrode arrays.
Conclusion: This study illustrates the ability to use an intracortical brain-computer interface with a fixed, LFP-based, simple decoder to analyze the spatial and temporal neural dynamics of human motor learning.

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Joshua Lin, MD, ScD, MPH, Medicine - General Internal Medicine

The impact of care-discontinuity on recording patient characteristics critical for comparative effectiveness and safety research when using electronic health records

J. Lin[1,2], R.J. Glynn[2], D.E. Singer[1] and S. Schneeweiss[2]

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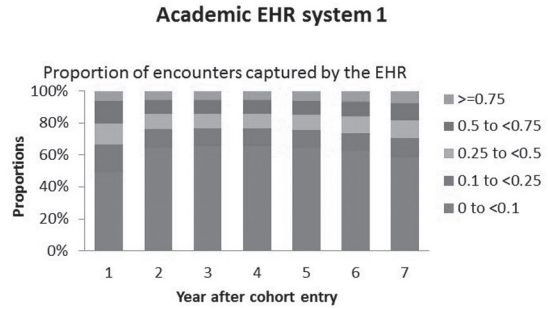
Introduction: Electronic health records (EHR) have been increasingly used for comparative effectiveness research. It is unclear how care-discontinuity, defined as receiving care outside of an EHR system, may affect data completeness and study validity using EHR. We aimed to quantify care-continuity of an EHR system and compare the misclassification of key variables in patients with high vs. low care-continuity.

Methods: Study cohort comprised all patients ≥ 65 in EHR from two large US provider networks linked with Medicare insurance claims data from 2007/1/1 to 2014/12/31. By comparing EHR and claims data, we quantified care-continuity by the **M**ean **P**roportion of **E**ncounters **C**aptured (**MPEC**) by the EHR system. Within levels of care-continuity, we quantified misclassification by **M**ean **S**tandardized **D**ifferences between the proportions of 40 key variables based on EHR alone vs. linked claims-EHR data ($\mathbf{MSD}_{_40_variables}$, <0.1 was used to indicate satisfactory variable classification). We compared patient characteristics in those with high vs. low EHR continuity.

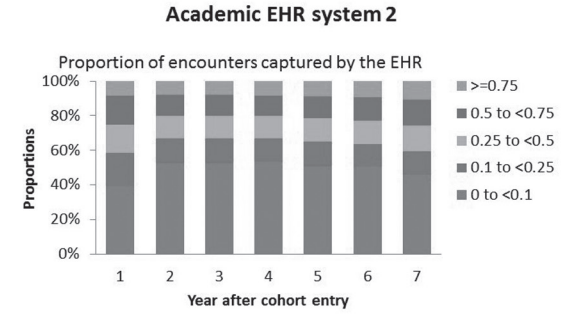
Results: Based on 104,403 patients in EHR system 1 and 79,336 in EHR system 2, the mean capture proportions of all records were 24% and 18% in system 1 and 2, respectively (Figure 1). The misclassification of key variables ($MSD_{_40_variables}$) based on EHR alone was 11.4-17.4 fold greater in those with lowest level of care-continuity (MPEC< 10%) than that in those with highest level of care-continuity (MPEC >= 80%), across EHR systems and years during follow-up (Figure 2). In both systems, capturing at least 60% of the encounters in an EHR was required to have satisfactory variable classification. The patient characteristics in those with high and low care-continuity were found to be comparable.

Conclusion: Care-discontinuity may lead to substantial misclassification in key variables. Researchers may consider restriction to those with high care-continuity to improve study validity when relying exclusively on EHR data.

Figure 1. Proportion of encounter captured by single EHR system by year after the initial encounter



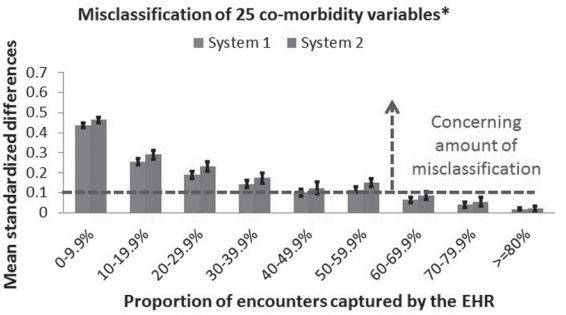
Total N	80,588	61,623	46,050	34,001	26,352	18,521	12,442
Capture%*	0.27	0.22	0.22	0.22	0.23	0.24	0.26

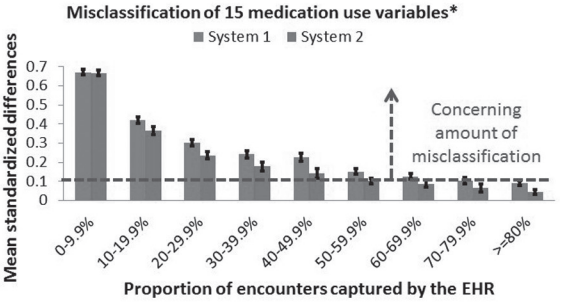


Total N	59,760	45,158	33,294	24,753	18,859	13,778	8,975
Capture%*	0.22	0.16	0.16	0.16	0.16	0.18	0.20

EHR= electronic health record, *Mean proportion of encounters captured by the EHR

Figure 6. Decreasing misclassification associated with increasing care-continuity





*See list of variables in Table 1

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Joshua Lin, MD, ScD, MPH, Medicine - General Internal Medicine

Identification of patients with high care-continuity to improve validity of comparative effectiveness and safety research using electronic health records

J. Lin[1], D.E. Singer[1], R.J. Glynn[2] and S. Schneeweiss[2]

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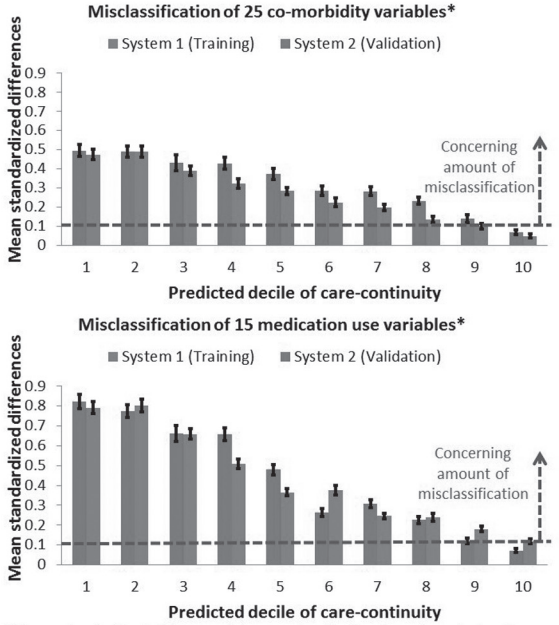
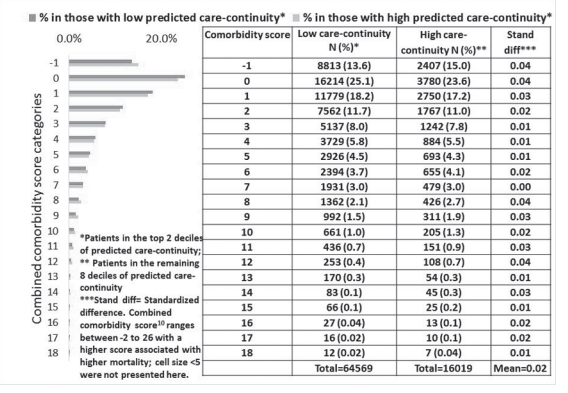
Introduction: Electronic health records (EHR) have been widely used for comparative effectiveness research. Care-discontinuity (i.e., receiving care outside of an EHR system) was associated with substantial information bias when using EHR as the sole data source. We aimed to develop and validate a prediction score for having high care-continuity to reduce such bias.
Methods: Study cohort comprised all patients ≥ 65 in EHR from two large US provider networks linked with Medicare insurance claims data from 2007/1/1 to 2014/12/31. Based on the linked EHR-claims data, we measured care-continuity by the **M**ean **P**roportion of **E**ncounters **C**aptured (MPEC) by the EHR system. With predictors available in EHR, we built a prediction model for MPEC by Lasso regression, using EHR system1 as the training and system2 as the validation set. Within deciles of predicted continuity, we quantified misclassification by **M**ean **S**tandardized **D**ifferences between the proportions of 40 key variables based on EHR alone vs. linked claims-EHR data ($MSD_{40_variables}$, <0.1 was used to indicate satisfactory variable classification). We compared patient characteristics in those with high vs. low predicted EHR continuity.
Results: Based on 104,403 patients in the training and 79,336 in the validation set, we developed a prediction score that was highly correlated with the measured care-continuity in both training and validation sets (Spearman correlation=0.81, 0.83, respectively). In the training set, $MSD_{40_variables}$ (misclassification based on EHR alone) in the worst predicted continuity decile was 7.8 (95% confidence intervals 6.8-9.1) fold greater than that in the best predicted continuity decile (Figure 1). Those with top 20% predicted continuity were found to have satisfactory variable classification ($MSD_{40_variables}$<0.1) and comparable patient characteristics, compared to the rest of population. We found similar results in the validation set (Figure 2).
Conclusion: Restriction to patients with high predicted care-continuity may reduce misclassification of key characteristics and improve validity of drug research relying exclusively on EHR.

Figure 4. Decreasing misclassification associated with increasing predicted care continuity



* Mean standardized difference between classification based on electronic health records (EHR) vs. the linked Claims-EHR data, see list of variables in Table 1

Figure 4. Representativeness: comparison of combined comorbidity score in those with predicted high vs. low care continuity in EHR system 1



Comorbidity score	Low care-continuity N (%)*	High care-continuity N (%)**	Stand diff***
-1	8813 (13.6)	2407 (15.0)	0.04
0	16214 (25.1)	3780 (23.6)	0.04
1	11779 (18.2)	2750 (17.2)	0.03
2	7562 (11.7)	1767 (11.0)	0.02
3	5137 (8.0)	1242 (7.8)	0.01
4	3729 (5.8)	884 (5.5)	0.01
5	2926 (4.5)	693 (4.3)	0.01
6	2394 (3.7)	655 (4.1)	0.02
7	1931 (3.0)	479 (3.0)	0.00
8	1362 (2.1)	426 (2.7)	0.04
9	992 (1.5)	311 (1.9)	0.03
10	661 (1.0)	205 (1.3)	0.02
11	436 (0.7)	151 (0.9)	0.03
12	253 (0.4)	108 (0.7)	0.04
13	170 (0.3)	54 (0.3)	0.01
14	83 (0.1)	45 (0.3)	0.03
15	66 (0.1)	25 (0.2)	0.01
16	27 (0.04)	13 (0.1)	0.02
17	16 (0.02)	10 (0.1)	0.02
18	12 (0.02)	7 (0.04)	0.01
	Total=64569	Total=16019	Mean=0.02

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Joshua Lin, MD, ScD, MPH, Medicine - General Internal Medicine

A Prediction Score for Anticoagulation Control Quality among Older Adults

J. Lin[1], D.E. Singer[1], R.J. Glynn[2] and S. Schneeweiss[2]

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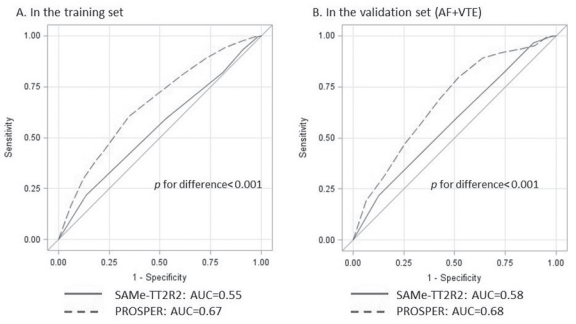
Introduction: Time in the Therapeutic Range (TTR) is associated with the effectiveness and safety of Vitamin K antagonist (VKA) therapy. To optimize prescribing of VKA, we aimed to develop and validate a prediction model for TTR in older adults on VKA for non-valvular atrial fibrillation (AF) and venous thromboembolism (VTE).

Methods: The study cohort comprised patients aged 65 and older on VKA for AF or VTE, identified in the two US electronic health record (EHR) databases linked with Medicare insurance claims data from 2007 to 2014. With the predictors identified in a systematic review and clinical knowledge, we built a prediction model for TTR, using one EHR system as the training and the other as the validation set. We compared the performance of the new models to that of a published prediction score for TTR, SAMe-TT2R2.

Results: Based on 1,663 patients in the training and 1181 in the validation set, our optimized score included 42 and the simplified model included 7 variables: (acronym: PROSPER:**P**neumonia, **R**enal dysfunction, **O**ozing blood [prior bleeding], **S**taying in hospital>=7 days, **P**ain medication use, no **E**nhanced [structured] anticoagulation services, **R**x for antibiotics). The PROSPER score outperformed SAMe-TT2R2 when predicting both TTR ≥70% (Area under ROC curve [AUC] 0.68 vs. 0.58 in the training, Figure 1) and the thromboembolic and bleeding outcomes (AUC 0.71 vs. 0.59, Figure 2) in.

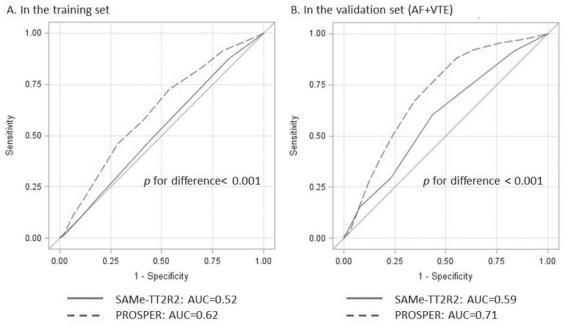
Conclusion: Our geriatric TTR score can be used as a clinical decision aid to select appropriate candidates to receive VKA therapy and as a research tool to address confounding and treatment effect heterogeneity by anticoagulation quality.

Figure 1. Comparison of AUC when predicting TTR>70%: PROSPER superior to SAMeTTR



AUC= area under the receiver operating characteristic, TTR= percent time in therapeutic INR range, AF= atrial fibrillation, VTE=venous thromboembolism

Figure 2. Comparison of AUC when predicting clinical outcomes*: PROSPER to SAMeTTR



* Composite outcomes of incident stroke, systemic embolism, venous thromboembolism, and major bleeding events; AUC= area under the receiver operating characteristic, TTR= percent time in therapeutic INR range, AF= atrial fibrillation, VTE=venous thromboembolism

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Yang Liu, MD, Surgery - General and Gastrointestinal

Inflammatory Properties of Ileal Fluid from Patients with IBD

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Introduction: Luminal contents play a crucial role in the induction and maintenance of intestinal inflammation. Patients with Crohn's disease benefit from diversion of the fecal stream, with immediate recurrence of inflammation after restoration of intestinal continuity. Furthermore, pouchitis after ileo-anal anastomosis for ulcerative colitis does not occur prior to ostomy closure. These observations support the premise that exposure to factors within the fecal stream is a critical component in inciting phenotypic expression of IBD. And, yet, the components within the fecal milieu that play a role in activating the inflammatory pathways still remain unknown. Recent data has demonstrated that levels of the anti-inflammatory mucosal defense factor Intestinal alkaline phosphatase (IAP) are reduced in colon biopsies of patients with IBD. Our central hypothesis is that pro-inflammatory factors in intestinal contents activate inflammatory cascades in the intestinal epithelial lining and that targeting these factors/pathways can present novel therapeutic approaches to treat IBD.

Methods: Ileal fluid samples from patients with and without IBD were collected from patients with an ileostomy seen in the surgical clinic at Massachusetts General Hospital, Boston. The effluent was centrifuged and the supernatant assayed by ELISA for key pro-inflammatory cytokines. Human THP1 macrophages were exposed to the fluid and assayed for cytokine

expression. IAP Activity was measured using the para-Nitrophenylphosphate (pNPP) assay. Demographics and clinical characteristics of patients were obtained from the medical records and correlated with inflammatory properties.
Results: Ileal fluid from 23 patients (15 IBD, 8 non-inflammatory controls) with a median age of 56 years (range; 29-94) was collected and assayed. TNF-a levels were significantly higher in ileal fluid of IBD patients than in controls (92.1 ± 29.9pg/ml vs. 33.6 ± 9.4pg/ml; $p = 0.03$) whereas IL-8 levels were similar (50.1 ± 11.9 vs. 35.3 ± 7.4; $p > 0.05$). IAP activity was significantly lower in patients with IBD than in patients without underlying inflammatory disease (14.6 ± 1.4 U/mg protein vs. 23.3 ± 2.2 U/mg protein; $p=0.002$). The inflammatory response of THP1 cells exposed to ileal fluid showed an individual cytokine profile for each patient and did not correlate with the cytokine levels in the original sample or the underlying disease. Further patient characteristics (e.g., gender, age, time of surgery) did not show any correlation with luminal ileal inflammatory properties.
Conclusion: Analysis of Ileal luminal contents showed significantly higher TNFa levels and lower IAP activity in patients with IBD. The individual inflammatory response profile of each patient could serve as a basis for determining the risk for recurring disease or pouchitis in stoma patients with IBD.

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Robert Lochhead, PhD, Medicine - Allergy/Immunology/Rheumatology

The inflammatory-proliferative synovial lesion in post-infectious Lyme arthritis results from impaired wound healing

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Introduction: Lyme arthritis (LA) is initially triggered by *Borrelia burgdorferi* infection, but in some patients, the synovitis persists despite 2-3 months of antibiotic therapy and spirochetal killing, called post-infectious LA. As in rheumatoid arthritis (RA), post-infectious LA is characterized by autoimmune inflammation and synovial hyperplasia. Our recent microRNA analysis revealed that antibacterial responses characterized the infectious phase of LA, and impaired wound healing may contribute to inflammatory and proliferative synovitis following resolution of infection. In mice, impaired wound repair and elevated interferon (IFN) responses during *B. burgdorferi* infection are associated with severe murine LA, but the role of impaired wound healing has not been explored in post-infectious LA or RA.
Methods: High-throughput RNA sequencing was performed using synovial tissue from patients with post-infectious LA (n=14), RA and other forms of inflammatory arthritis (n=8), and osteoarthritis (OA, n=5), and analyzed using in-house and online bioinformatics tools. Cells expressing IFNG were identified by intracellular cytokine staining and flow cytometry of cells collected from fresh synovial tissue and synovial fluid. Immunofluorescent (IF) microscopy was used to identify IFNG-responsive cells from patient synovial biopsies.
Results: 1001 genes were differentially expressed (DE) in post-infectious LA synovial tissue compared with OA tissue, of which 517 (43%) were interferon-regulated genes (Table 1). In addition, 85/190 (45%) of genes in the response to wounding gene ontology (GO) set were DE in post-infectious LA patients compared with OA patients (Figure 1). Of these, ~1/3 were involved in coagulation, cell proliferation/differentiation, and extracellular matrix (ECM) formation, and were down-regulated in post-infectious LA, but less consistently in RA; whereas ~2/3 were involved in immune activation, IFN responses, and ECM degradation, and were up-regulated in both post-infectious LA and RA, compared with OA. Cytotoxic $CD8^+$ T cells were a major source IFNG in post-infectious LA and RA synovial tissue, and fibroblasts within foci of active synovitis expressed high levels of IFNG-inducible HLA-DR molecules.
Conclusion: These data show that impaired wound healing is a previously unrecognized component of the inflammatory-proliferative synovial pathology of post-infectious LA and RA. We propose that dysregulated wound healing in inflamed tissue may potentiate break in immune tolerance during the early stages of autoimmune development. Thus, post-infectious LA provides a natural human model of infection-induced autoimmunity, in which impaired wound healing leads to autoimmune synovial pathology of the chronic inflammatory arthritides, including RA.

Table 1. Interferome analysis of differentially-expressed (DE) genes in synovial tissue of patients with post-infectious LA, compared with OA.

DE genes LA vs. OA	IFN-regulated	Other
Up in LA vs OA	363 (48%)	397 (52%)
Up in OA vs LA	154 (35%)	287 (65%)
Total DE genes	517 (43%)	684 (57%)

Number (and percentage) of interferon (IFN)-regulated genes or other (non-IFN-regulated) genes differentially-expressed (DE, adj. p-value<0.05) in synovial tissue from patients with post-infectious LA, compared to patients with OA.

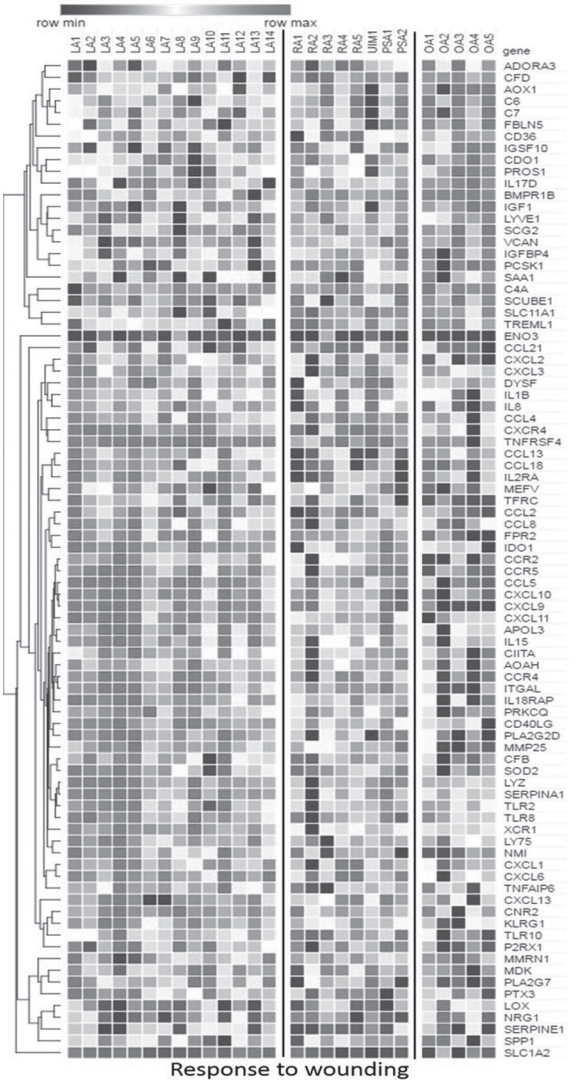

Figure 1. Response to wounding gene ontology (GO) pathway analysis. Hierarchal clustering of log-transformed expression of 85 differentially-expressed genes (adj. p value<0.05) associated with response to wounding (GO category 0009611, Princeton Univ.) in synovial tissue from patients with LA (n=14), other forms of inflammatory arthritis (n=8), and osteoarthritis (n=5). Analysis performed using 1-Pearson correlation metric and average linkage method (Morpheus, Broad Institute).

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Katie Love, Masters in Chemistry, Medicine - Cardiology

The Burden of Ventricular Ectopy in Mitral Valve Prolapse

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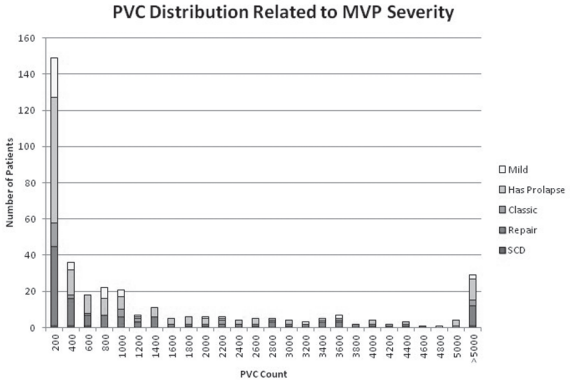
Introduction: Mitral Valve Prolapse (MVP) is a common heart condition that affects 2-3% of the population, however many questions remain regarding the disease pathophysiology and epidemiology. There is evidence for a genetic basis for the disease and MVP can be associated with other cardiac events and abnormalities including Sudden Cardiac Death (SCD) and arrhythmias. Not all patients with MVP will require corrective surgery during their lifetime. For uncommon events such as SCD, there are no well-established clinical predictors to identify patients at risk. However, a "malignant" form of MVP has been proposed which includes frequent premature ventricular contractions (PVCs) and an elevated risk of SCD. The number of PVCs has not been previously studied in large MVP cohorts as a predictor of outcome. We aimed to assess the distribution

of PVC burden in a large cohort of MVP patients seen at the Massachusetts General Hospital. In particular, we were interested in exploring whether there is a subset of MVP patients with a high PVC burden or PVC distribution is a continuum.
Methods: We used the RPDR Query tool along with a custom designed processing algorithm (Python) to parse through candidate subjects' cardiology reports. We searched all outpatients visiting MGH between 1/1/2015 – 12/31/2016 for the presence of MVP on an MGH echocardiogram. From this collection of 2043 patients with mitral valve prolapse, 367 patients were identified who also had Holter Monitoring. The PVC burden was extracted from these Holter reports for further analysis. MVP due to Marfan's syndrome was excluded.
Results: The results show that the PVC burden in patients with MVP spans a wide range, primarily concentrated at a low PVC count (fewer than 200 PVCs). However a subset of patients with MVP (7.9%) had a high PVC burden (>5000 PVCs per 24 hours). Interestingly, a trend was observed with a greater proportion of subjects with high PVC burden who had undergone mitral valve surgery compared to those with low (<200) PVC burden ($p = 0.1$).
Conclusion: These data suggest that there is an identifiable sub-population of MVP patients who have a high PVC burden. Additional characteristics of this population may include a greater likelihood of having undergone surgical correction of the MVP. Further study of this sub-population will be of interest to determine whether they have a higher risk of SCD.



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Pan Lu, M.D, Anesthesia, Critical Care and Pain Medicine

Cyclophilin D-associated anesthetic-induced cognitive impairments in the developing brains

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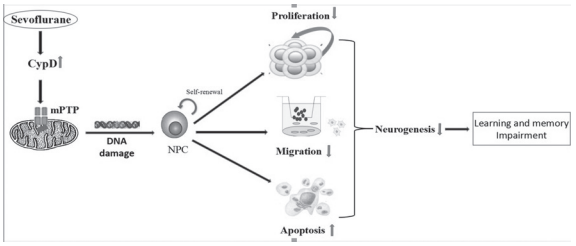
Introduction: Children who have multiple exposures to anesthesia and surgery may have an increased risk of developing a learning disability. Our previous studies showed that anesthetic sevoflurane induced cognitive impairment and inhibited neurogenesis. However, the underlying mechanism remains largely unknown. Cyclophilin D (CypD), a component of mitochondrial permeability transition pore (mPTP), is critical for cognitive function. Therefore, we set out to assess whether sevoflurane inhibits neurogenesis via CypD/mPTP-regulated reduction in neural progenitor cells (NPCs) proliferation and migration, increase in NPCs apoptosis and disturbance in NPCs differentiation, leading to cognitive impairment in young mice.
Methods: Wild-type (WT) and CypD knockout (KO) mice received 3% sevoflurane 2 hours daily for 3 days from postnatal day (P)6 to P8. We administered 5-Bromo-2'-deoxyuridine (Brdu) (50 mg/kg) to the mice 30 minutes before each of the sevoflurane anesthesia. We then assessed the effects of the sevoflurane on neurogenesis and cognitive function was determined by using immunohistochemistry and Morris Water Maze. NPCs harvested from WT and CypD KO mice were treated with 4.1% sevoflurane for 6 hours. We then determined the mitochondrial functions, DNA damage, proliferation of the NPCs using flow cytometer, migration by transwell assay and differentiation by immunofluorence, Western blot, and immunocytochemistry, respectively.
Results: The sevoflurane anesthesia decreased Nestin- and Brdu-positive cells in the brain slices of P8 or P31 mice, and increased the CypD levels, induced opening of mPTP, caused DNA damage, decreased NPC proliferation in hippocampus, inducing cognitive impairment in the WT mice. Sevoflurane anesthesia decreased NPC proliferation and migration in vitro, as well as cause cognitive impairment in mice. These effects were mitigated by knockout of CypD mice and in CypD KO NPCs.

Conclusion: These data suggest that sevoflurane may increase CypD level, which then causes mPTP opening, leading to DNA damage of NPCs. The damaged DNA decreases NPC proliferation, inhibition NPC migration, ultimately leading to cognitive impairment in the young mice.



The hypothetical pathway

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Shu Y. Lu, MD, Anesthesia, Critical Care and Pain Medicine

Association of nutritional deficit with functional status at the time of discharge from the intensive care unit in critically ill surgical patients

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Introduction: Low functional status at the time of discharge from the intensive care unit (ICU) is increasingly being recognized as a risk factor for long-term morbidity and short-term mortality in critically ill patients. Although nutrition is often thought of as a modifiable risk factor for adverse outcomes in hospitalized patients, the relationship between nutritional deficit and functional status has not been well characterized in ICU patients. Therefore, we sought to determine if there was an association between nutritional deficit over the course of critical illness and functional status at the time of ICU discharge among critically ill surgical patients.
Methods: We performed a retrospective analysis of data from two surgical ICUs at the Massachusetts General Hospital. Nutritional deficit was categorized as either caloric or protein deficit during ICU length of stay (LOS), and estimated using the American Society of Enteral and Parenteral Nutrition guidelines. Functional status was assessed using the Functional Status Score for the ICU (FSS-ICU) within 24 hours of ICU discharge. To investigate the association of caloric deficit with FSS-ICU, we constructed a linear regression model controlling for age, sex, race, body mass index (BMI), Acute Physiology and Chronic Health Evaluation (APACHE) II score, and ICU LOS. A similar model was constructed to investigate the association of protein deficit with FSS-ICU.
Results: 976 patients comprised the analytic cohort. Mean age and BMI were 62 ± 16 years and 28 ± 7 kg/m2, while the mean APACHE II score was 18 ± 8. For every 281 kcal (280.81; 95%CI 119.72 – 441.91) increase in caloric deficit, there was a unit decrement in FSS-ICU score. Similarly, for every 18g (17.56; 95%CI 7.81-27.10) increase in protein deficit, there was a unit decrement in FSS-ICU score.
Conclusion: In our cohort of surgical patients, nutritional deficit over the course of critical illness was inversely associated with functional status at the time of discharge from the ICU. Future studies are needed to determine whether aggressive nutritional supplementation can improve functional status in critically ill patients.

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Cara Lucke, BA, Psychiatry

Assessing Differences in Mental Health Screening by Region Before and After Implementation of an Innovative Statewide Program for Children with Medicaid

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Introduction: Massachusetts implemented the Children's Behavioral Health Initiative (CBHI) which contains mandates for routine pediatric behavioral health (BH) screening as well as outpatient services for children in need. Several studies have documented substantial increases in both screening and outpatient BH services over the eight years of the program consistently across race, ethnicity, and language. Because prior CBHI research had already documented a lack of racial/ethnic disparities in rates of screening and rates of positive screening, the current study explored potential differences in rates of screening and rates of positive screening among children residing in different geographic regions of Massachusetts.
Methods: We assessed differences in rates of screening and of positive screening for children (4-17 years) in three cohorts of about 2000 cases of pediatric outpatients seen before (2007) and after (2010, 2012) the start of CBHI. Data were from chart reviews supplemented by administrative claims data.
Results: The current study confirmed previously published reports of a major increase in the use of formal screening tools from 2007 (<5%) to 2010 and 2012 (>70%). Although there were increases in rates of screening in all regions from 2007 to 2010 and 2012, there were consistent significant differences in these rates. The Western and Southeastern regions demonstrated the highest rates of screening in both 2010 and 2012 (~77-89%) while the Northeast and Metro West regions demonstrated the lowest rates of screening (~61-68%). There were also consistent significant differences in rates of positive screenings in both 2010 and 2012, with the Central and Boston regions having the lowest rates of positive screens (~4-8%) and the Northeast and Metro West regions having the highest rates of positive screens (~23-33%).
Conclusion: The current study demonstrated that previously reported increases in formal screening with the advent of the CBHI applied to children and adolescents regardless of geographic region in Massachusetts. Although all geographic regions showed increases in formal screening after CBHI, there were nevertheless significant and persistent differences in rates of screening and positive screens by region. Interestingly, the Northeast and Metro West regions demonstrated significantly lower rates of screening but significantly higher rates of positive screens among those who were screened. Further work to assess whether these differences in screening are associated with differences in service utilization and health outcomes is warranted.

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Maria Lucia Madariaga, MD, Surgery - Thoracic

Angiography before resection of posterior mediastinal tumors: selection criteria, tumor embolization and spinal artery collaterals

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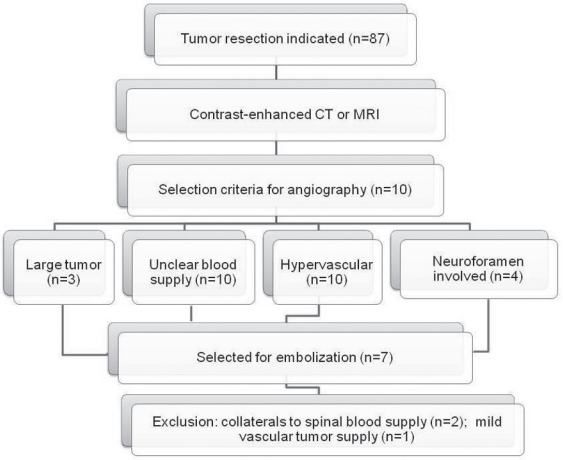
Introduction: Resection of posterior mediastinal tumors may be complicated by bleeding or neurologic injury. Preoperative spinal angiography of mediastinal tumors has been underreported or not commonly practiced. This study evaluates the selection criteria and outcomes of patients with posterior mediastinal tumors who undergo preoperative angiography and embolization.
Methods: Single-institution retrospective study of patients with posterior mediastinal tumors from 2002-2016. Multi-level spinal angiography was performed with or without selective arterial embolization of vascular supply in patients selected by thoracic or neurologic surgeons.
Results: Ten (11%) of 87 patients with posterior mediastinal tumors underwent preoperative angiography (Figure 1). A mean of 11 (range 2-25) arteries were studied. Embolization in 7 of 10 patients successfully occluded 1 to 3 arteries. There was no significant difference in age, gender, BMI, ASA class, operative time, operative blood loss, complications or mortality between patients with or without angiography. Patients who underwent angiography had larger tumors (1490 vs. 97 cm^3, $p<0.0001$), involvement of the neuroforamen (44% vs. 10%, $p<0.05$) and longer hospital stay (9 vs. 4.5 days, $p<0.05$). Angiography was complicated in 1 patient by vocal cord ulceration after intubation of a tumor-compressed trachea. Shared blood

supply between tumor and spinal cord precluded embolization and tumor resection in 1 patient. Utilization of angiography increased over time.
Conclusion: Selective preoperative angiography for evaluation of posterior mediastinal tumors identifies arterial variations, threatened spinal arteries and targets for embolization, but can be associated with significant complications. The specific role of embolization requires further investigation to standardize indications and number of arteries examined.



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Elizabeth N. Madva, MD, Psychiatry

A Care Management Intervention for Non-Cardiac Chest Pain: A Pilot Project

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Introduction: Chest pain is a common presenting complaint in both general practice and emergency room settings. The possibility of a life-threatening etiology often prompts urgent or emergent evaluation. Importantly, the majority of these cases (as high as 80 percent) do not have underlying coronary artery disease and about half also do not have an alternative medical diagnosis (such as GERD). This non-cardiac chest pain can persist, cause distress, impair function, and lead to recurrent medical evaluation. This pilot project aims to evaluate the degree of psychological distress and functional impairment in this population and to determine whether a nurse-led care manager intervention, with physician support, can improve symptoms and function.
Methods: We plan to enroll 12 patients found to have a non-cardiac etiology for their persistent chest pain on stress testing or cardiac catheterization. A nurse care manager will contact patients two weeks after initial assessment to confirm whether chest pain symptoms have persisted and if so, will schedule a collaborative in-person consultation visit with a cardiologist, nurse care manager, and psychiatrist. Baseline measures evaluating psychiatric symptoms (Patient Health Questionnaire-9, Generalized Anxiety Disorder-7, Patient Health Questionnaire-15), quality of life (Short Form Health Survey-12, Patient-Reported Outcomes Measurement Information System-10), and the severity, frequency, and impact of chest pain will be completed, with the ultimate goal to assess the most likely cause(s) of the chest pain. Following the office visit, recommendations for further diagnostic evaluation and treatment will be communicated to the patient's primary care physician. The nurse care manager will call the patient weekly for four weeks and then bimonthly for eight weeks to provide education, reassurance, support, and therapeutic interventions, and will coordinate with the team psychiatrist as needed if a psychiatric condition is present. At the conclusion of the 3-month period, patients will repeat baseline measures to evaluate improvement in psychiatric symptoms, quality of life, and chest pain symptomatology. Measures of feasibility and acceptability will also be completed.
Results: Recruitment is ongoing.
Conclusion: Prior work has shown that non-cardiac chest pain is common, can cause distress and impaired function, and can lead to recurrent medical evaluation. More work is needed to determine the most effective management techniques for this unique and high-morbidity population.

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Rajshri Mainthia, MD, Surgery

Malpractice claims after cholecystectomy: what factors are associated with plaintiff payout?

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Introduction: Complications following cholecystectomy, one of the most common procedures performed by general surgeons, can carry significant morbidity and rank among the leading sources of medical malpractice claims against surgeons. Given the overall emotional, physical, and financial costs of malpractice claims to patients, providers, and the health care system, we aimed to study characteristics of claims involving surgical management of benign biliary disease and identify factors associated with plaintiff payout.

Methods: A retrospective cohort study examining closed malpractice claims involving surgical management of benign biliary disease over 20 years (1995-2015) was performed using the CRICO Strategies' Comparative Benchmarking System database, the largest detailed database of paid and unpaid malpractice claims in the world. A total of 745 cases were isolated; of these cases, claim characteristics were studied, univariate analysis was performed to compare characteristics across paid and unpaid claims, and a multivariable model was used to determine factors predicting claim outcome.

Results: Claims related to surgical management of benign biliary disease (n=745) accounted for 18.3% of all general surgery malpractice claims. The most common allegation was "improper performance of surgery" and the most common contributing factor was an "issue with technical skill." The most common associated complications included bile duct injury (n=397), bowel perforation (n=96), hemorrhage from an adjacent structure (n=55), and major vascular injury on trocar insertion (n=23). When a bile injury occurred, it was only recognized intraoperatively 18.6% of the time and definitive management of the injury most often involved biliary reconstruction surgery (77.3% of cases). The average time from event to case close was over 3 years. Approximately 40% of claims (n=290) resulted in plaintiff payout; of these cases, all but one claim were settled out of court and the average cost per claim was $265,000. For the remaining claims not resulting in plaintiff payout (n=455), most cases were denied, dropped, or dismissed (n=443) while 14 claims resulted in a defense verdict after trial. The total administrative and legal costs for claims in which there was no patient payout averaged $11,000 per claim. On multivariable analysis, shortened time from event to claim, bile duct injury, bowel perforation, and high clinical severity were associated with plaintiff payout ($p<0.05$). On both univariate and multivariable analysis, a resident or fellow being named in a case was negatively predictive of plaintiff payout ($p<0.05$).

Conclusion: Complications during cholecystectomy carry significant morbidity and clinical strategies that reduce the risk and aid in earlier recognition of complications should be a priority. In this large sample, only 40% of malpractice claims relating to cholecystectomy complications resulted in payout to patients and all but one case was settled out of court. This suggests that surgeons may also have an opportunity to improve discussions about the risks of complications as well as to advance their support of patients and families when a complication occurs. This may lead to earlier resolution of claims and a reduction in litigation burden for both patients and surgeons.

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Sara J. Makaretz, BS, Neurology

FTP tau PET imaging in semantic variant Primary Progressive Aphasia

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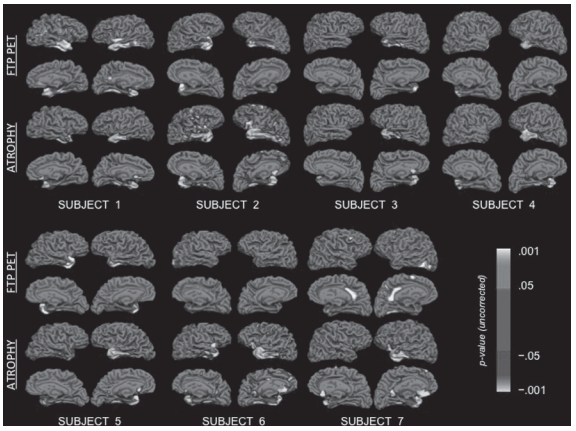
Introduction: The semantic variant of Primary Progressive Aphasia (svPPA) is a form of PPA that is typically associated with Frontotemporal Lobar Degeneration (FTLD) with long TDP-43-positive neuropil threads and dystrophic neurites (FTLD TDP-43 Type C pathology), and is only rarely due to a primary tauopathy or Alzheimer's Disease (AD). We undertook the present study to investigate the uptake, localization, and magnitude of the presumed tau PET tracer [18F]Flortaucipir (FTP;

formerly known as T807 or AV1451) in a series of patients with semantic variant PPA, with the hypothesis that most patients would not show tracer uptake appreciably different from controls.

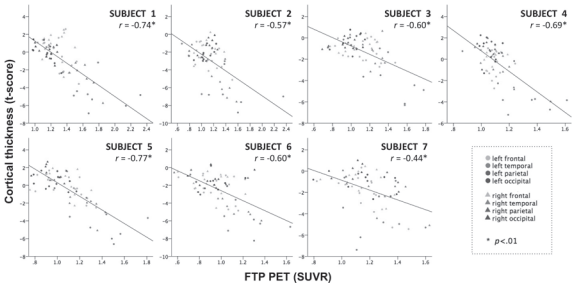
Methods: FTP and [11C]PiB brain PET imaging as well as MRI imaging was performed in a series of 7 patients with svPPA (mean age = 66.0) and in 20 age-matched, amyloid negative controls. T1-weighted structural MPRAGE images were reconstructed using FreeSurfer (FS) version 6.0.0. Each subject's PET images were co-registered to their structural MRI data, and primary analyses of PET data were performed without partial volume correction (PVC), then repeated with PVC. For each svPPA subject, we performed a surface-based, whole-cortex general linear model (GLM) analysis to compare the thickness of the patient's cortex at each vertex point across the entire cortical mantle to the group of controls. Similarly, we performed a GLM comparing FTP signal in the individual patient at each vertex point to FTP signal in the group of controls. Within each patient, Pearson correlation analyses were performed across 64 FS ROIs to assess the relationship between FTP signal and cortical thickness t-scores ("atrophy").

Results: All 7 patients showed elevated FTP uptake in the anterior temporal lobe with a leftward asymmetry and magnitude that was not observed in healthy controls. This elevated FTP signal was largely co-localized with regions of neurodegeneration, evident on both visual inspection and quantitative cortical surface-based analysis. For each patient, correlation between cortical thickness t-score and FTP SUVR showed medium to large effects for both uncorrected FTP SUVR (Case 1, -.740; Case 2, -.572; Case 3, -.600; Case 4, -.686; Case 5, -.769; Case 6, -.598; Case 7, -.435) and PVC FTP SUVR values (Case 1, -.779; Case 2, -.627; Case 3, -.643; Case 4, -.733; Case 5, -.771; Case 6, -.568; Case 7, -.661), where ROIs with higher FTP signal also showed more atrophy. Of the 7 patients included in this series, 5 were amyloid negative, 1 was amyloid positive (Case 7), and 1 has an unknown amyloid status (Case 2).

Conclusion: In this series of patients with clinical profiles, structural MRI, and amyloid PET imaging typical for svPPA, FTP signal was unexpectedly elevated with a spatial pattern localized to areas of atrophy and presumed neurodegeneration. The absence of elevated amyloid biomarkers in all but one of these patients indicates that these patients do not likely have AD pathology with paired helical filament tau inclusions. Therefore, the modest elevations in FTP co-localized and correlated with atrophy demonstrate either FTP binding to straight filament tau in the context of a primary tauopathy, or non-specific binding co-localized with neurodegeneration in the context of TDP pathology. Based on the field's collective experience in clinicopathologic studies of patients with this syndrome (>90% with TDP-43 pathology), it seems most likely that our findings point toward FTP binding to a molecule(s) associated with neurodegeneration other than tau. Further investigation with autopsy analysis will help illuminate the binding target(s) of FTP in cases of suspected FTLD-TDP neuropathology.



At the individual subject level, the distribution of increased FTP SUVR (red-yellow) and cortical atrophy (blue) are highly overlapping. Surface maps represent vertices with significant differences in measure of interest, as identified with t-tests comparing each subject to the control group. P-values are uncorrected. For each subject, the top two rows show FTP SUVR images, and the bottom two rows show cortical atrophy.



Relationships between cortical atrophy and FTP SUVR measured in 68 cortical ROIs for each individual svPPA patient. In each patient, the magnitude of regional FTP SUVR signal is robustly correlated with magnitude of cortical thickness abnormality (cortical thickness t-score for each region compared to a group of cognitively normal participants). Each point on each scatterplot represents the values from a single cortical region of interest, color coded by lobe and separated by hemisphere. Note the consistent presence of the temporal lobe regions in the lower right of each scatterplot.

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Jennifer Makin, MD, Emergency

A ketamine package impact on access, compassionate care, and affordability in support of emergency and essential gynecological operations when no anesthetist is available

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Introduction: One of the primary barriers to accessing emergency and essential surgeries in low- and middle-income countries is the lack of access to anesthesia services. In 2011, a study of the Nyanza Region of Kenya revealed that 57% of hospitals equipped with an operating theatre, perioperative human resources, and a doctor who could perform cesarean sections, had severe difficulty in accessing anesthesia services when needed. This study analyzed all gynecologic operative procedures within a larger database, on the use of a novel ketamine package (ESM-Ketamine) in support of emergency and essential operative procedures when no anesthetist was available, in rural Kenya.
Methods: Non-anesthetist clinicians in Kenya underwent five days of training on ESM-Ketamine, complemented by check-lists, wall charts, and ESM-Ketamine kits. Pre-, intra-, and postoperative details were captured on all cases. The primary outcome was whether the ESM-Ketamine package could safely support emergency and essential gynecologic surgeries and procedures when no anesthetist was available
Results: Non-anesthetist ESM-Ketamine providers from eight study facilities supported 208 emergency and essential gynecological surgeries and procedures. There were no ketamine- related serious adverse events. Brief (less than 30 seconds) oxygen desaturations (below 92%) and hallucinations occurred in 4.8% and 12.5% of cases, respectively. In 11% of the non-training cases, women would have refused care if the only option had been to pay for an anesthetist, and prior to ESM-Ketamine, 21.9% of the non-training cases would have been performed without analgesia, sedation, or anesthesia.
Conclusion: This study provides promising preliminary evidence that the ESM-Ketamine package is a safe alternative when no anesthetist is available and may increase the availability, quality, and affordability of painful gynecological procedures in resource-limited settings. The ESM-Ketamine package may allow for improved compassionate care and greater access to life-saving and life-improving procedures for women when no anesthetist is available.

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Ann M. Malley, PhD, Medicine - MGH Cancer Center

Older Adults 'and Family Caregivers' Perspectives Regarding Their Preoperative Care Transitions

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Introduction: Older adults living with multiple chronic conditions, coupled with advances in surgical technology, are challenging our health care system to provide safe perioperative care. Increased age and higher rates of obesity contribute to an increased prevalence of osteoarthritis and a greater need for surgical procedures such as joint replacement. Joint replacement represents the singles largest cost center for CMS and there can be extreme variability in cost and outcome. Nearly fifty percent of adults over age 65 years have three or more chronic illnesses and more than 20 % live with more than five chronic conditions. Older adults with one or more chronic conditions tend to have a greater likelihood of disability and those with multiple chronic conditions tend to use a greater number of healthcare services which makes coordination of care more difficult for these individuals. Compounding the difficulties of reconciling instructions of multiple providers, patients with multiple chronic conditions are often less able to participate effectively in their own care. This can lead to suboptimal care. Family caregivers (accounting for up to 30 % of the US adult population) are often left to navigate care systems on behalf of the older adult care recipient. As family caregivers are largely responsible for ensuring that plans are followed, it is critical that family caregiver engagement occurs as older patients experience transitions on care. Patient engagement (IOM, 2011) is a critical component of care necessary for improving patient outcomes. As patient variability drives patient outcome it is critical that we recognize individual patient needs, preferences and capacities in the preoperative environment through effective patient engagement. Little is known about how older adults with multiple chronic conditions and their family caregivers engage in preoperative care transitions and the subsequent impact of this experience on postoperative health outcomes. The purpose of this study was to describe how older patients with multiple chronic conditions and their family caregivers perceive their engagement and overall care experience throughout the preoperative phase of elective orthopedic hip or knee joint replacement.

Methods: Prospective, qualitative descriptive design using semi-structured telephone interviews with a convenience sample of older adults coping with multiple chronic conditions and their family caregivers. Interviews, conducted prior to surgery and again 21 days post-surgery, were audio recorded and transcribed for qualitative content analysis.
Results: Eleven patients and 5 family caregivers participated. The Quality Health Outcomes Model includes Client-System-Intervention-Outcome indicators and proposes that dynamic relationships with indicators not only act upon but reciprocally affect various outcomes. The effect of an intervention is mediated by client and system characteristics. Guided by the Quality Health Outcomes Model, four major themes were identified. CLIENT: Older adults are often highly engaged preoperatively as they perceive that joint replacement is about quality of life. SYSTEM: Standardized preoperative care can compromise patient engagement and often does not address the unique preoperative needs of complex older adults. INTERVENTION: Family caregivers (by default) become the mediators or primary care coordinators for older adults. OUTCOME: There can be large variability in the post-operative care trajectory and resource utilization for older adults with multiple chronic conditions having elective joint replacement.
Conclusion: Joint replacement outcomes can be influenced by patient characteristics; but perhaps are also reflective of a system where embedded standardized care interventions are received with uncertainty by the complex older adult and mediated by the patient and family caregiver with variability. This uncertainty and variability influences the level of patient preparedness and engagement and may be influencing the overall care trajectories and resource utilization for those most vulnerable well beyond the perioperative episode of care. In recognizing that certain surgical procedures such as joint replacement represent an opportunity to improve a patient's quality of life, the Centers for Medicare & Medicaid Services (CMS, 2015) has focused on these procedures in response to the variability of the quality and cost of these types of procedures. Depending on the provider and where the treatment takes place, the quality and cost of these types of joint replacements can vary. Of note, the CMS Bundled Payment for Joint Replacements (CCJR) *episode of care will start on the day a traditional Medicare beneficiary is admitted for joint replacement*. The first transition in care for patients undergoing elective joint replacement arguably occurs when the patient confers with an orthopedic surgeon and the decision is made to have surgery. Hence, this initial or preoperative phase of care becomes the genesis of the care trajectory for the perioperative joint replacement patient. Therefore, it is critical for stakeholders to identify and utilize evidence based metrics in the preoperative phase of care to ensure optimal transitions on admission and throughout the perioperative care trajectory. Current preoperative care interventions are often standardized to achieve organizational efficiency and are often not designed to effectively engage complex older patients and their family caregivers. Coordinated patient-centered preoperative care that reflects the needs and goals of complex older patients and their family caregivers may positively influence outcomes and reduce resource utilization.

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Mohammad Mansouri, MD-MPH, Radiology

Deep Learning for Rapid, Accurate, Automated Detection & Characterization of Intracranial Hemorrhage on Unenhanced Head CT

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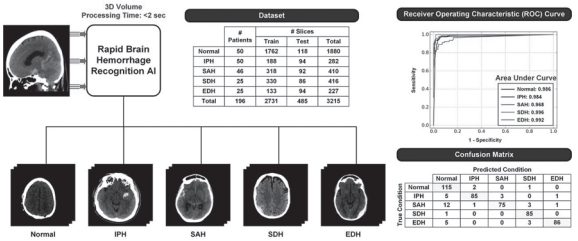
Introduction: To develop & validate a rapid, accurate, fully-automated brain hemorrhage deep learning (DL) based assessment tool, to assist clinicians in the detection & characterization of intracranial hemorrhage (ICH) - including subarachnoid hemorrhage (SAH), intra-parenchymal hemorrhage (IPH), epidural and subdural hematoma (EDH & SDH).
Methods: In this retrospective HIPAA-compliant IRB-approved study, our PACS system was searched for unenhanced head CTs of IPH, SAH, & SDH/EDH from 2010-2016. Two radiologists reviewed the scans and selected slices with hemorrhage for training. The training set was enriched with cases that had subtle or small volume bleeds. We additionally randomly selected 100 slices from each class for validation, independent of the training set. Full resolution 512x512 pixel CT images were converted into gray levels by applying a brain CT window setting (window-level = 50 HU, window-width = 100 HU). We applied transfer learning methodology using a customized (weight initialized) ImageNet pre-trained Convolutional Neural Network (CNN), fine-tuned on our training dataset.
Results: A total of 1880 normal, 410 SAH, 282 IPH, 416 SDH, and 227 EDH head CT slices were collected from 50 normal, 46 SAH, 50 IPH, 25 SDH, and 25 EDH patients. Area Under the Receiver Operating Curve (AUROC) for detection of hemorrhage was 0.99 for normal patients, 0.97 for SAH, 0.98 for IPH, 0.99 for SDH, and 0.99 for EDH. The deployment time for full head CT 3D-volume assessment was less than 2-sec (mean) for all slices.
Conclusion: Despite our relatively small number of training cases enriched with small, subtle bleeds, our transfer learning approach using a customized pre-trained CNN achieved relatively high accuracy for the detection & characterization of intracranial hemorrhage.



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Melissa C. Maravic, PhD, MPH, Psychiatry

Preliminary Baseline Findings from the PCORI Pragmatic Trial "Integrated Smoking Cessation Treatment for Smokers with Serious Mental Illness"

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Introduction: Addiction to nicotine is highly prevalent among those with serious mental illness (SMI). Recent estimates indicate that 64%-79% of those with schizophrenia spectrum disorders smoke tobacco regularly, as do 44-71% of those with bipolar disorder, and 43% of those with major depressive disorder. Despite the extensive evidence that most smokers with SMI want to quit smoking and that first-line pharmacotherapies for smoking cessation specifically for those with SMI are efficacious and well tolerated, few with SMI are offered advice to quit smoking or are prescribed proven effective tobacco dependence pharmacologic and behavioral treatment by their primary care providers (PCP). This 3-year study aims to test the effect of academic detailing (AD) (a provider-level educational intervention focused on evidence-based smoking cessation treatment for those with psychiatric illness), alone or in combination with practical support from a community health worker (CHW), on the provision and utilization of smoking cessation treatment to those with SMI and, to determine if these interventions improve smoking cessation rates for smokers with SMI.

Methods: This study is currently enrolling smokers with SMI who receive psychiatric rehabilitation services from one of two agency partners, Bay Cove Human Services or Vinfen Corporation. Participants complete a 5-minute baseline survey (Year 1) about their smoking habits and the care they had received from their primary care doctor in the last year, followed by a carbon monoxide (CO) breath test. Participants will be asked to complete this survey on two more occasions, on an annual basis, after the intervention has been implemented (Years 2 and 3). Following the completion of baseline data collection in August 2017, primary care clinics that provide care to these smokers will be randomly assigned to receive AD to their PCPs about smoking cessation for people with SMI or treatment as usual. Participants who receive primary care through clinics assigned to the AD intervention will be randomized to be offered support from a CHW (AD+CHW) or not (AD).

Results: To date, 971 smokers with SMI have been enrolled in the study and have completed the baseline survey. Preliminary baseline results indicate that 70.3% of the population is male. Most participants (46.4%) self-identify as white, followed by Haitian, Black or African American (35.7%). The majority of participants smoke 11-20 tobacco products per day (32.7%), with an average expired CO reading of 22.5 ± 20.6 (n=889) and reported smoking within 5 minutes of waking (39.9%). On average, the smokers in this sample scored a 2.89 ±1.67 (n=966) on the Heaviness of Smoking Index, a measure indicating low to moderate dependence. Eight hundred ninety-seven participants (92.7%) reported that their PCP is aware they smoke tobacco products and 71.4% reported that their PCP recommended they quit smoking. The most commonly reported prescribed or suggested smoking cessation treatment was the nicotine patch (72.9%), followed by the nicotine gum/lozenge (51.2%), varenicline (16.3%) and bupropion (3.9%). Six hundred and sixty-five participants (68.5%) reported having one or more current or past smoking-related health condition. Participants most commonly reported their general health as good (35.0%), followed by fair (24.4%).

Conclusion: Preliminary baseline data indicate that the participants in this sample are moderate smokers with low to moderate dependence on nicotine. While the PCPs providing care to these smokers are largely aware that their patients smoke, few have offered first-line pharmacological treatment for smoking cessation.

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Sandro Marini, MD, Center for Human Genetic Research (CHGR)

Control of ethnically-stratified vascular risk factors in modeling of intracerebral hemorrhage

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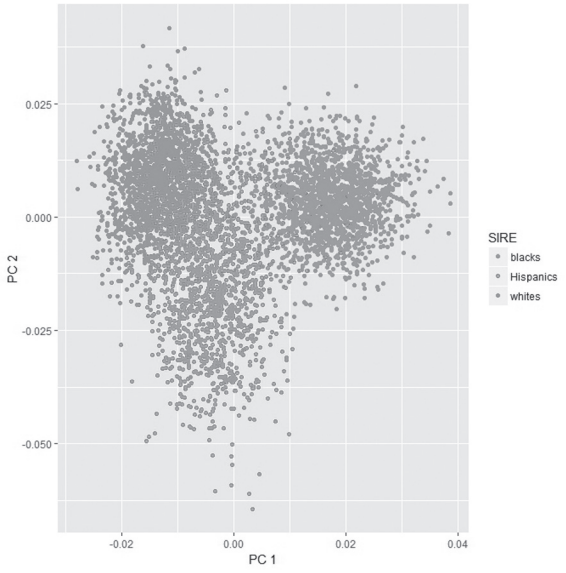
Introduction: Prevalence of vascular risk factors (VRFs) and their net effects vary across ethnic populations. We hypothesized that use of DNA-based ancestry informative markers (AIMs), compared with self-reported race/ethnicity, would result in better prediction of VRF status in U.S. minority populations and thus provide greater accuracy in attributing risk of intracerebral hemorrhage (ICH) across racial/ethnic groups.

Methods: Using data from the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study (a multi-center case-control study of ICH in whites, blacks, and Hispanics), we utilized 15 ancestry-informative single nucleotide polymorphisms (SNPs) to perform principal component (PC) analysis using PLINK v1.9 variance-standardized relationship matrix dimension reduction. Logistic regression (adjusted for age) and tests of two independent samples (X^2 and Mann-Whitney U tests) were used to compare PC-defined ancestry with self-identified race/ethnicity in association with VRFs. Results of sub-analyses within each population were further meta-analyzed to highlight differences between self-identified classifications. Finally, we compared two models for ICH risk (one with self-reported ancestry, one with AIMs), adjusting for age and hypertension.

Results: Among 4,935 subjects (median age 61, interquartile range 52–72), 34.7% were blacks, 35.1% white, and 30.2% Hispanic. Percentages of hypertension, hypercholesterolemia, and diabetes differed across self-identified race/ethnicity as well as PCs (all $p < 0.001$). However, even within each self-reported population, PC dispersals [CA1] differed among those with and without each of the VRFs ($p < 0.001$). Regression of each VRF with PCs, adjusting for age, confirmed independent associations of PCs with both hypertension and diabetes exposures ($p < 0.001$). Akaike information criterion (6303 vs. 6321) and Davidson-MacKinnon J test ($p < 0.001$) verified that PC-defined ancestry significantly improved the ICH risk prediction model over self-identified ancestry alone.

Conclusion: AIMs provide a more detailed assessment of risk exposures in studies employing representative U.S. populations. Particularly among Hispanics and blacks, the use of AIMs adds value over self-reported ancestry in controlling for genetic and environmental exposures unique to these populations. This more inclusive ancestry modeling may be a useful tool to improve risk prediction accuracy.



Dimensional plot of principal components (PC) grouped by SIRE (self-identified race and ethnicity)

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Haley L. Marks, PhD, Dermatology

An Oxygen-Sensing Phosphorescent Liquid Bandage for Post-Operative Flap Monitoring

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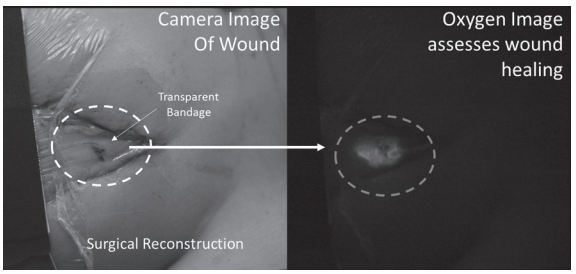
Introduction: Non-invasive monitoring of the transcutaneous partial pressure of oxygen ($tcpO_2$) has great potential as the new standard of care in post-operative monitoring of autologous free flaps following cancer, trauma, or other reconstructive surgeries. Tissue perfusion and oxygenation are critical performance measures in the assessment of wound healing and graft monitoring; however, current clinical methods using near-infrared spectroscopy to probe the tissue's oxygen saturation (StO_2) from the local vasculature obscure the skin, require a wired hardware connection, and are ultimately an indirect measure.
Methods: We demonstrate how a dye-embedded liquid bandage, when painted on the flap skin paddle of four women undergoing a deep inferior epigastric artery perforator (DIEP) flap reconstruction after mastectomy, can be used to visualize tissue oxygenation using a simple commercial DSLR camera. Our transparent paint-on bandage formulation consists of New-Skinâ liquid bandage, an oxygen-sensing metallo-porphyrin exhibiting bright red phosphorescence, and the green-fluorescing reference dye fluorescein.
Results: Red and green filtered photographs of the bandage were acquired for 48 hours post-operatively, and temporal changes in phosphorescence corresponding to $tcpO_2$ were compared directly to StO_2 readings obtained from a standard near-infrared tissue oximeter (ViOptix) placed on the same flap.
Conclusion: Preliminary results show that the relative phosphorescence intensity reported by the liquid bandage inversely correlates with the stO_2 values provided by the current gold standard of care, the ViOptix, as expected, while being substantially less obtrusive and enabling visualization of the flap beneath, even in patients with high melanin content, providing an additional advantage over current methods.



The transparent bandage worn on the breast glows brightly under blue excitation to yield tissue oxygenation information.

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Felisha A. Marques, MPH, Medicine - General Internal Medicine

A Qualitative Inquiry of Physician and Patient Experiences with Shared Decision Making

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Introduction: Shared decision making (SDM) is the interactive process between patients and clinicians that engages patients in decision-making, reviews relevant treatment and screening options, and tailors treatments to patients' goals. Since 2005, Massachusetts General Hospital (MGH) has promoted SDM and the use of decision aids, mainly in the primary care clinics. This project collected qualitative data to support enhancements in clinician training and improvements for the use of SDM in routine clinical care.
Methods: We conducted individual interviews in person and by phone with clinicians and patients at MGH who had prior experiences with SDM. Our recruitment target was six clinicians and four patients. Semi-structured interview questions asked participants about their knowledge of SDM and the challenges and barriers associated with implementation of SDM. Responses were transcribed from recorded interviews, and analyzed for recurring themes.
Results: Eight clinicians and five patients were interviewed. The clinician sample was comprised of primary care physicians, specialty care physicians, a physician assistant, and a medical student. Clinicians had an average of just over 13 years

of practice, with a range spanning 29 years. All indicated at least some level of experience in conducting shared decision making conversations with patients. Interviews with clinicians typically lasted between 25-45 minutes. The patient sample was comprised of three males and two females, with an average age of 69 and an age range of 52 years. Clinicians had similar working definitions of SDM, and understood the benefits of SDM approaches in clinical care, but also identified barriers to implementation which aligned with those already in the literature. Major themes included time and patient knowledge as barriers, areas to improve SDM training, and patient empowerment. Patients' limited knowledge about their medical condition and perception of their role in the provider-patient relationship were both noted by clinicians as a barrier to SDM. One clinician noted that some patients underestimate risks and overestimate benefits. One patient stated: *"I relied more on what they said. The paperwork can say anything they want, but when the doctor suggests there are different risks and different options, and they've gained your confidence. They all know more than me, so I relied almost exclusively on their recommendations. And I was more than comfortable with that."* Patients generally did not have a formal understanding of SDM. Multiple patients, when asked, did not attempt to define the process, stating they either didn't know how to define it, or instead asked the interviewer to define it for them first. Despite this, two patients believed that their doctors had engaged in shared decision making with them in the past. Clinicians highlighted existing gaps in shared decision making training, or potential new areas in which to promote shared decision making training. Clinicians noted that they could benefit from an increased awareness of shared decision making concepts and available decision aids. Two clinicians also stressed the importance of focusing on training that is practice-based, rather than simply didactic learning through lectures. One primary care physician stated: *"When we were all being trained, SDM wasn't a part of the curriculum. I don't even think the phrase was there."* Clinicians believed that a more formal training for health care professionals could better facilitate shared decision making between patients and providers, particularly patients with limited literacy, mental health disorders, and substance abuse disorders.

Conclusion: These interviews support a need to address barriers for incorporating SDM as a part of routine clinical care. If made routine, shared decision making could help increase patient satisfaction and health outcomes. Successful integration of SDM can better support overall health outcomes and improve patients' experiences of care.

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Elena Maryamchik, MD MBA, Pathology

Rivaroxaban Causes Missed Diagnosis of Protein S Deficiency but not of Activated Protein C Resistance (Factor V Leiden)

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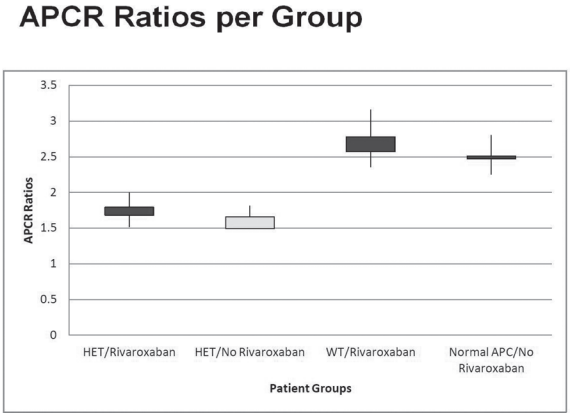
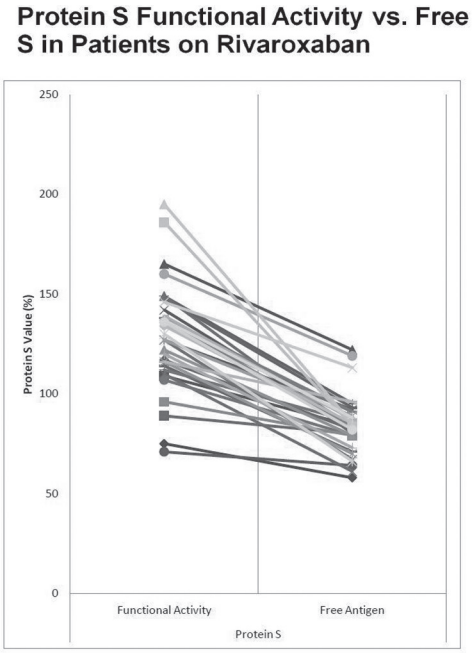
Introduction: Factor V Leiden (FVL) is the most common inherited risk factor for venous thromboembolic disease. The activated protein C resistance (APCR) test is a clot-based assay for detecting FVL. One study in rivaroxaban-spiked plasma from 10 volunteers showed that rivaroxaban caused an artefactual increase in the APCR ratio. However, there is no sufficient data as to whether the elevated values can cause a missed diagnosis of FVL, and no data in patients taking rivaroxaban using the most common APCR test method. Another study found rivaroxaban can falsely elevate protein S activity. We sought to determine if rivaroxaban could mask a diagnosis of protein S deficiency or FVL, to determine the magnitude of these problems in a "real world" patient population, and to establish recommendations for FVL and protein S testing of patients on rivaroxaban.

Methods: We prospectively analyzed hypercoagulation panels of all patients encountered by our Special Coagulation Laboratory over 2.5 years. Four groups of fifteen patients were identified (n=60 total): patients heterozygous for FVL (FVL-HET) taking rivaroxaban, wild type patients taking rivaroxaban, FVL-HET not taking rivaroxaban, and wild type patients not taking rivaroxaban. All patients on rivaroxaban were tested for protein S activity and free protein S antigen (n=32). Geometric mean APCR ratios of the four groups, and geometric mean protein S activity vs. free antigen were analyzed using Student's t-test. P values <0.05 were considered statistically significant.

Results: FVL-HET/taking rivaroxaban had lower APCR than normal patients ($p<0.0001$). FVL-HET/taking rivaroxaban mean APCR was 1.75(+/- 0.12), versus 1.64(+/-0.3) in FVL-HET/not taking rivaroxaban (P=0.005). APCR in FVL-HET/taking rivaroxaban fell more than 3 standard deviations below the cutoff of 2.2 at which the laboratory reflexes FVL DNA testing (heterozygous patients have been invariably ≤ 2.0 in our laboratory). No cases of FVL were missed despite rivaroxaban. The increase in APCR of the wild type patients taking rivaroxaban compared to wild type patients not taking rivaroxaban was not statistically significant (P=0.07). Rivaroxaban concentration ranged up to a high-therapeutic level of 349 ng/mL rivaroxaban (anti-Xa 1.51 u/mL by a LMWH curve). Testing protein S in patients on rivaroxaban showed that rivaroxaban falsely elevates protein S activity, regardless of the presence or absence of FVL ($P<0.0001$). Four of the 32 patients had low protein S free antigen results (range 58-67%), whereas protein S activity was falsely normal in all four cases (range 75-130%),

p<0.01. Therefore, unlike APCR, rivaroxaban would have caused a missed diagnosis of all four cases of protein S deficiency that we encountered in rivaroxaban patients over a 2.5 year period, when using a protein S activity assay.
Conclusion: The APCR assay is able to distinguish FVL-HET patients taking rivaroxaban from normal patients at the cut off of 2.0. We propose that a cut-off of 2.2 renders indiscriminate DNA testing of all patients on rivaroxaban unnecessary. An anti-Xa assay can be considered to exclude supratherapeutic rivaroxaban, because supratherapeutic rivaroxaban patients were not encountered in this study. Free protein S antigen should be tested in patients on rivaroxaban in order to exclude a hereditary protein S deficiency, with the caveat that protein S activity testing would need to be performed after rivaroxaban has been discontinued in order to detect the rare type II protein S deficiency.





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Charles Masaki, MD, PhD, Emergency

A ketamine package in support of emergency and essential obstetric and gynecologic operative procedures in severely resource limited settings when no anesthetist is available

C. Masaki[1,2,3], J. Makin[1,2,3], G. Wuyke[3], A. Senay[1], D. Suarez-Rebling[1], J. Imbamba[3], J. Juma[3], K. Rogo[3], M. Guha[1,3] and T.F. Burke[1,2,3]

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Introduction: In low resource settings, anesthesia services are often unavailable even in the presence of functional operating theatres, adequate surgical equipment, peri-operative services and staff capable of performing surgical procedures. Obstetric and gynecologic operative procedures are among the most commonly performed surgical procedures globally. Lack of access to life-saving obstetric and gynecological operative procedures in severely resource-limited settings, such as in complex humanitarian crises, has been associated with adverse maternal and newborn health. In fact, lack of access to cesarean section is often the greatest surgical gap in times of complex humanitarian emergencies. Additionally, in humanitarian crises, anesthesia services are often non-existent and thus a critical barrier to accessing cesarean section and other life-saving and life-improving surgical procedures. The aim of this study was to examine a series of obstetric and gynecologic emergency and essential operative procedures supported by an innovative anesthesia package, called Every Second Matters for Emergency and Essential Surgery - Ketamine (ESM-Ketamine) TM, designed for use when no anesthetist is available.
Methods: The ESM-Ketamine package includes a best evidence clinical pathway, an intensive five-day training program and a defined ESM-Ketamine kit complemented by wall-charts and pocket checklists. The ESM-Ketamine clinical pathway includes a standardized pre-operative evaluation as well as defined pre-induction tasks such as vital signs assessment, initiation of intravenous access, pre-oxygenation, and placement of pulse oximetry and blood pressure monitoring devices.

Induction into a dissociative state is accomplished via 2mg/kg of intravenous ketamine administered over 30-60 seconds. One to 2 mg/kg doses of ketamine are administered every 10-15 minutes as needed to maintain the dissociative state. Ketamine-related side effects are managed via diazepam for hallucinations and/or agitation, promethazine for nausea, atropine for hypersalivation and hydralazine for peri-partum hypertension. Non-anesthetist clinicians from hospitals located among four severely resource limited counties in Kenya underwent five-days of training on ESM-Ketamine. Data were collected prospectively each time ESM-Ketamine was invoked in support of an operative procedure. All obstetric and gynecologic operative procedures supported by ESM-Ketamine were analyzed.

Results: Between November 4, 2013 and February 22, 2017, the ESM-Ketamine package was used to support 923 emergency and essential operative procedures, 444 (48.1%) of which were obstetric or gynecologic in nature. Among the 444 cases, 149 (33.6%) were training cases and 295 (66.4%) obstetric and gynecological surgical cases supported by an ESM-Ketamine provider. Among the 295 non-training cases, the ESM-Ketamine pathway was invoked in support of 134 (45.4%) emergency surgical procedures when no anesthetist was available, 105 (35.6%) of which were emergency cesarean sections and laparotomies. In sixty-eight (23.1%) cases, the ESM-Ketamine pathway was invoked because delay in carrying out the surgical procedure would have resulted in compromised care. Fifty-eight (19.7%) of the procedures were deemed minor, for which an anesthetist would previously not have been called. Seventeen (5.8%) women reportedly could not afford an anesthetist and initially refused surgery, only consenting when support from ESM-Ketamine was offered. The reason for invoking the ESM-Ketamine pathway was not documented in 18 (6.1%) cases. There were no Ketamine related serious adverse events. Oxygen desaturations (below 92%) for less than 30 seconds occurred in 15 (3.4%) cases, and 80 (18.0%) were administered diazepam to treat hallucinations or agitation.

Conclusion: The ESM-Ketamine package appears safe for use in support of emergency and essential obstetric and gynecologic operative procedures in severely resource-limited settings.

ESM – KETAMINE™ SAFETY CHECKLIST

For emergency/essential surgery and procedural sedation

☐ Complete ESM-Ketamine Clinical Record

☐ Confirm ketamine concentration

☐ Confirm equipment function

- Pulse Oximeter
- Blood Pressure Device
- Oxygen Source/Facemask
- Suction
- Bag Valve Mask

☐ Place IV of normal saline

☐ Place pulse oximeter onto the same side as the IV

☐ Place blood pressure cuff on arm opposite the pulse oximeter and IV

☐ Place oxygen on patient

☐ Titrate appropriate IV ketamine dosing:

1) Emergency/Essential surgery:
   - 2 mg/kg initially over 30-60 seconds
   - 1-2 mg/kg every 10-15 minutes
2) Procedural Sedation:
   - 1 mg/kg initially over 30-60 seconds
   - 0.25-1 mg/kg additionally as needed

☐ Complete ESM-Ketamine Clinical Record

ESM- Ketamine Pocket Checklist (front page) showing the ESM-Ketamine clinical pathway

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Sean J. Matuszak, BA, Orthopedics

Predictors of Periprosthetic Acetabular Radiolucency Progression in Midterm Follow-up of Metal-on-Metal Hips

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Introduction: Osteolysis is an aseptic, inflammatory reaction characterized by periprosthetic bone loss, which was a major concern in early THA devices. A leading reason for the introduction of metal-on-metal (MoM) bearings was purported low wear rates, theoretically leading to reduced osteolysis. However, recent registry studies have shown that aseptic loosening secondary to osteolysis is still a leading cause of implant failure in patients implanted with these bearings. Data on predictors of development or progression of osteolysis and radiolucency in MoM implants remains limited despite the ubiquity of radiographs in follow up. The aim of the current work is to describe the nature of osteolytic lesion progression and to identify predictors of progression in patients treated with MoM THA and HRA at midterm follow up.

Methods: Patients were selected from a prospective, international clinical registry of the Articular Surface Replacement (ASR) Hip System. The ASR bearing surface was available as MoM HRA (ASR HRA) and as MoM THA (ASR XL THA). Annual follow-up of patients included anteroposterior (AP) radiographs, patient-reported outcome measures (PROMs), and whole blood cobalt (Co) and chromium (Cr) ion level measurements. Patients meeting the following criteria were included in the present analysis: at least two sequential AP radiographs from follow-up visits with a minimum six months between radiographs, no contralateral implant regardless of bearing surface, complete reported demographics, and reported implant information. All patients consented to be followed in this IRB-approved study. A total of 805 patients were included in this study (541 MoM HRA, and 264 MoM THA). Radiographs were analyzed by five orthopedic surgeons with a minimum five years of clinical experience who were blinded to clinical results. Radiolucency was defined as a lesion with a clear sclerotic border at least 1 mm in width, and osteolysis was defined as a radiolucency over 2 mm in width. Osteolytic lesion progression was defined as any lesion developing *de novo*, or an existing lesion progressing from radiolucency to osteolysis between the two radiographs. MoM HRA and MoM THA were considered separately for all statistical analyses. Clinical variables and PROMs from the enrollment interval were tested for univariate and multivariate correlation with osteolytic lesion progression.

Results: The median time between radiographs was 2.0 years (Range 0.5-4.3). The number of cases with any osteolysis or radiolucency was 50 (6.2%) at enrollment and 110 (13.7%) at midterm follow up, representing a twofold increase. The distribution of osteolysis and radiolucency for MoM HRA and MoM THA are shown in Figure 1. Osteolytic lesion progression was found in 97 of 805 patients (12.0%). More predictors were identified for MoM HRA than for MoM THA. Univariate analysis revealed that high Cr ($p = 0.015$), high Co ($p = 0.018$), and low version angles ($p=0.006$) were correlated with osteolytic lesion progression in MoM HRA. No variables were significant in MoM THA single variable tests. Multivariate analysis revealed that Co or Cr over 5ppb ($p = 0.034$, OR = 2.312) was an independent predictors of lesion progression in MoM HRA. Higher UCLA activity scores were a predictor ($p = 0.033$, OR = 1.344) of osteolytic lesion progression in in the multivariate model for MoM THA. Multivariate model results are shown in Table 1.

Conclusion: In conclusion, physicians of patients implanted with MoM HRA implants should pay careful attention to patients with higher ion chromium levels, higher cobalt levels, and lower version angles. Indicators for MoM THA remain unclear, although a higher UCLA activity score may be a risk factor. Physicians should carefully monitor any MoM patients with the appropriate predictors for osteolysis progression through midterm followup, and possibly consider them for early revision.

Results of binary logistic regression for each implant group considering the outcome of osteolytic lesion progression

ASR HRA			ASR XL THA		
Variable	p-value	Odds Ratio (95% Confidence Interval)	Variable	p-value	Odds Ratio (95% Confidence Interval)
Age	0.172	1.023 (0.990-1.056)	Age	0.303	0.981 (0.944-1.018)
Sex (male)	0.406	1.346 (0.667-2.715)	Sex (male)	0.392	0.683 (0.286-1.634)
Years to enrollment	0.915	0.990 (0.832-1.180)	Years to enrollment	0.366	0.866 (0.633-1.183)
Years between visits	0.155	1.328 (0.890-1.061)	Years between visits	0.614	0.861 (0.483-1.537)
Abduction angle	0.339	1.020 (0.980-1.061)	Abduction angle	0.542	1.018 (0.961-1.078)
Co or Cr over 5 ppb	0.034	2.312 (1.064-5.022)	Co or Cr over 5 ppb	0.594	1.275 (0.523-3.107)
UCLA activity score	0.850	1.015 (0.871-1.183)	UCLA activity score	0.044	1.275 (1.006-1.616)

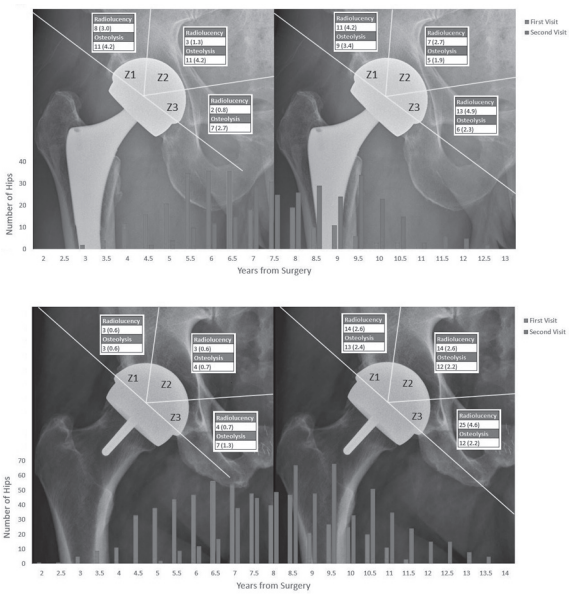

Figure 1 - osteolysis and radiolucency distributions from enrollment to midterm followup for ASR XL THA (top) and ASR HRA (bottom).

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Anne Marie McCarthy, PhD, Medicine - General Internal Medicine

Impact of *PIK3CA* tumor mutation on the association of aspirin or NSAID use and time to breast cancer recurrence

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Introduction: Aspirin or NSAID (A/N) use post diagnosis is associated with lower risk of breast cancer recurrence and mortality in cohort studies. A potential mechanism is that A/Ns may suppress cell growth and induce apoptosis in tumors driven by phosphatidylinositol 3 kinase (*PIK3CA*), the most common oncogene mutation in breast cancer. An interaction of A/Ns and *PIK3CA* mutation has been observed for colorectal cancer prognosis, but has not been studied in breast cancer. The objective was to assess time to breast cancer recurrence (TTR) with respect to A/N use and *PIK3CA* mutation.

Methods: Patients with HR+/HER2- breast cancer treated at Massachusetts General Hospital in 2009-2014 who received tumor genotyping were included. *PIK3CA* mutations, including 8 common hotspot mutations, were assessed by a high-throughput tumor genotyping assay using DNA from formalin-fixed, paraffin-embedded tumor tissue. A/N use beginning 6 months post diagnosis through metastasis was extracted from electronic medical records using coded data and natural language processing. Patients with de novo metastatic disease or progressive disease within 6 months of primary diagnosis were excluded. TTR was estimated using Cox proportional hazards models.

Results: Among breast cancer patients (N=212), 60 (28%) used A/Ns and 69 (33%) had *PIK3CA* mutation (see Table). After adjusting for age, stage, adjuvant endocrine therapy, radiation, and chemotherapy, A/N users had significantly longer TTR (HR=0.65 p=0.01). The association was similar for wild type (HR=0.58 p=0.01) and *PIK3CA* mutated tumors (HR=0.60 p=0.06), with no significant interaction of A/N use and *PIK3CA* (p=0.34).

Conclusion: Among HR+ breast cancer patients, those who used A/Ns following primary diagnosis had longer TTR than non-users, regardless of tumor *PIK3CA* mutation status. The study provides a model for how tumor genomics could be integrated into secondary chemoprevention studies.

Time to recurrence adjusted for age, stage, and treatment

		N	HR	95% CI	p-value	p-interaction
A/N user		60	0.65	0.46-0.91	0.01	
PIK3CA mutation		69	0.81	0.59-1.11	0.11	
A/N use	PIK3CA mutation					
-	-	102	Reference			0.34
+	-	41	0.58	0.38-0.88	0.01	
-	+	50	0.75	0.52-1.07	0.11	
+	+	19	0.60	0.35-1.02	0.06	

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Christopher McGovern, BA, Psychiatry

Frequency of Cannabis Use is Associated with More Symptoms of Cannabis Dependence Only among Those with Higher Levels of Trait Impulsivity

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Psychiatry, Massachusetts General Hospital, Somerville, MA, USA

Introduction: The past decade has seen an increase in the rate of cannabis use in the United States, with 18-25 year olds representing the age group most likely to use cannabis. Despite the disproportionate number of individuals in this age group who use cannabis compared to other age brackets, only 5.1% of 18-25 year old cannabis users meet criteria for a cannabis use disorder. This suggests that there are determinants beyond frequency of cannabis use that put an individual at risk for a cannabis use disorder. This study examined interactions between frequency of cannabis use and dimensions of impulsivity as independent and interactive predictors of symptoms of cannabis use disorder.

Methods: A community sample of 75 regular cannabis users (at least once a week), aged 18-25 years, was enrolled. Baseline assessments included self reported past 90-day cannabis use, obtained with a modified timeline follow-back procedure; cannabis use disorder, assessed with the Cannabis Use Disorder Identification Test – Revised (CUDIT-R), an eight item screening measure that assesses cannabis use and associated problems over the last six months; and impulsivity, assessed with the Urgency, Premeditation, Perseverance, Sensation-Seeking and Positive Urgency (UPPS-P) Impulsive Behavior Scale. The UPPS-P is a 59 item self-report measure that includes five subscales: negative urgency, (lack of) premeditation, (lack of) perseverance, sensation seeking, and positive urgency. Higher scores suggest higher levels of impulsivity.

Results: Multiple linear regression models were conducted with CUDIT-R total score as the dependent variable. Independent variables included past 90 day cannabis use frequency, UPPS-P scores, and their interactions. All models controlled for age, sex, and age of cannabis use initiation. In all models, the main effects of past 90-day cannabis use frequency and impulsivity were not significant (p-values > 0.05). However, the interactions between cannabis use frequency and impulsivity were significant for sensation seeking ($t=2.02$, $p=0.047$), premeditation ($t=2.15$, $p=0.04$), and perseverance ($t=2.12$, $p=0.04$). Simple slope analyses revealed that more frequent cannabis use was associated with more symptoms of cannabis dependence, but only among those reporting more sensation seeking ($t = 3.58$, $p=0.001$), less premeditation ($t = 4.18$, $p<0.001$), and less perseverance ($t = 3.71$, $p<0.001$). There were no interactions between frequency of cannabis use and positive and negative urgency on dependence symptoms (frequency x positive urgency: $t = -0.64$, $p=0.52$; frequency x negative urgency: $t = -0.09$, $p=0.93$).

Conclusion: Results show that individuals who use cannabis more frequently may be at greater risk for experiencing symptoms of cannabis dependence, but only if they also report higher levels of trait impulsivity. Further, only individuals who are more likely to be drawn to novel, intense experiences, and are less likely to plan for the future and persist in the face of adversity may be more vulnerable to the adverse consequences of frequent cannabis use. Impulsivity in the context of positive and negative affect does not appear to increase the association between frequent cannabis use and cannabis use disorder. This study shows that not all frequent users develop cannabis use disorder, helping differentiate specific subgroups of individuals most at risk for problematic use and informs the development of more targeted prevention efforts.

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Jenna McNeill, MD, Medicine - Pulmonary

Does the time of day a Pulmonary Embolism Response Team (PERT) is activated affect time to intervention or outcome?

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Introduction: A multidisciplinary Pulmonary Embolism Response Team (PERT) has been developed to assess high risk pulmonary embolism cases and provide rapid treatment recommendations. This team can be activated via 24 hour/ 7 day a week phone communication. In this study we evaluated the effect of the time of activation of PERT on: the number of interventions, time to intervention, 30-day mortality.

Methods: Study population: Patients with proven pulmonary embolism (PE) for whom PERT was activated between 10/2012 to 03/2016. "Day" and "night" activations were defined as those occurring between 06:00 and 20:59 and 21:00 and 05:59, respectively. "Intervention" was defined as a treatment in addition to anticoagulation occurring within 24 hours of PERT activation, including: systemic intravenous thrombolysis, catheter directed thrombolysis, surgical thrombectomy and ECMO. "Early intervention" was defined as occurring within 6 hours of the PERT activation. Continuous variables were compared between the two groups using t-tests or Wilcoxon rank sum tests and categorical variables were compared using chi-square or Fisher's exact tests.

Results: Of 467 PERT activations, 10 were excluded due to intervention prior to PERT activation. Among the remaining 457 activations, 317 occurred during the day and 140 during the night. There were 42 (13%) and 21 (15%) interventions within 24 hours of activation for the day and night groups, respectively. The median time to intervention was shorter for the day group vs. the night group (5.6 hours (3.6-15.5 hours) and 12.8 hours (4.4-14.1 hours) respectively, p=0.28). Similarly, the day group was more likely to have an intervention within 6 hours (23 vs. 6 interventions, respectively, p=0.06). Specifically, catheter directed thrombolysis was more likely to occur within 6 hours in the day vs. night group. Despite the differences in timing of intervention, there was no significant difference in 30-day mortality between the day and night groups (12% vs. 16%, p = 0.32).

Conclusion: In patients with PE, the likelihood of an intervention was affected by the time of day the PERT was activated. Despite similar clinical characteristics, patients in who PERT was activated during the night appeared to have a delay in the time to catheter based intervention.

Characteristics of Day and Night Groups

	Day	Night	P Value
All patients	N=317	N=140	
Age (in years), Mean (SD)	62(16)	61(5)	0.50
Female gender, N(%)	140(44)	71(51)	0.20
Race, N(%)			
White	266(84)	108(77)	0.16
African American	25(8)	13(9)	
Asian	4(1)	3(2)	
Hispanic	8(3)	2(1)	
Other	14(4)	14(10)	
Highest heart rate, Mean (SD)	106(22)	107(23)	0.74
Lowest systolic blood pressure, Mean (SD)	115(24)	115(21)	0.76
Highest respiratory rate, Mean (SD)	22(5)	23(7)	0.14
Troponin Value, Median (Q1-Q3)	0.03(0.01-0.12)	0.04(0.01-0.11)	0.30
BNP value, Median (Q1-Q3)	877(215-3001)	1313(356-3810)	0.93
Simplified Pesi Score, Median (Q1-Q3)	1 (1-2)	1(0-2)	0.81
30 day mortality, N(%)	36(12)	19(16)	0.32

Treatment within the Day and Night groups

	Day	Night	P value
Interventions within 24 hours of activation, N (%)	42(13)	21(15)	0.62
Among patients with treatments within 24 hours of activation (N=63)			
Type of treatment, N(%)			0.056
Systemic IV Thrombolysis	12(29)	2(10)	
Catheter based	23(55)	17(81)	
Surgical embolectomy	7(17)	1(5)	
ECMO	0(0)	1(5)	
Time to intervention (hours), Median (Q1-Q3)			
All	5.6(3.6-15.5)	12.8(4.4-14.1)	0.28
Systemic IV thrombolysis	3.4(2.6-10.0)	2.2(0-4.4)	0.41
Catheter based	7.6(4.2-21.5)	13.5(8.7-16.3)	0.59
Surgical embolectomy	5.8(4.3-10.2)	4.0	0.38
ECMO		12.8	-
Interventions within 6 hours of activation, N (%)	23(55)	6(29)	0.063
Among patients with treatments within 6 hours of activation (N=29)			
Type of treatment, N(%)			0.99
Systemic IV thrombolysis	9(39)	2(33)	
Catheter based	10(43)	3(50)	
Surgical Embolectomy	4(17)	1(17)	
ECMO	0(0)	0(0)	

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Arielle Medford, MD, Medicine - Hematology/Oncology

HER2 mutations detected by ctDNA in ER+/HER2- metastatic breast cancer patients: incidence and impact on clinical outcomes.

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Introduction: While the human epidermal growth factor receptor 2 (HER2) gene has long been linked with the pathogenesis and prognosis of breast cancer, its significance has been recognized only when the receptor has been amplified. However, rare, but actionable, somatic mutations in HER2, without HER2 gene amplification, have been described in breast cancer based on molecular analysis of metastatic specimens (frequency ~1%). Little is known about the incidence, which is determined by blood-based genotyping assays, nor the impact of HER2 mutations on clinical outcomes in patients with ER+/HER2- metastatic breast cancer (MBC).
Methods: We evaluated the presence of HER2 mutations based on routine tissue and blood-based genotyping assays, ordered by treating oncologists at our institution, for patients with estrogen receptor positive (ER+)/HER2 negative MBC. The tissue analysis was based on SNAPSHOT-NGS, an anchored multiplex polymerase chain reaction assay that detects single nucleotide variants (SNV) and insertions/deletions (indel), and the blood-based genotyping analysis was based on circulating tumor DNA (ctDNA) detection using the Guardant 360 panel, a next-generation sequencing (NGS) assay capable of detecting mutations with comparable sensitivity to SNAPSHOT. Patients with acquired HER2 mutations were identified, and multivariate analysis was performed to evaluate the hazard ratio (HR) for the association between HER2 mutations and progression free survival (PFS), adjusting for age and number of prior therapies.
Results: Among the ER+/HER2- MBC patients (N=118), 11% (N= 13) were found to have acquired HER2 mutation by ctDNA analysis, but no HER2 mutations were identified in any patients based on tissue-based molecular analysis of archival specimens. Among patients with HER2 mutant, ER+/HER2- MBC, the median age at metastatic diagnosis was 57.34 (range 51.5-67.1) years, 7.7% had de-novo metastatic disease, and 30.8% had prior CDK 4/6 inhibitor therapy. In terms of outcomes, in the multivariate model, patients with HER2 mutant breast cancer had similar PFS when treated with endocrine and targeted therapy combination (HR = 0.24; p = 0.21), and trended towards worse PFS with chemotherapy (HR = 2.69; p = 0.06), as compared to non-HER2 mutant group, albeit duration of follow up was limited (median duration = 6.7 months). Of note, most of the detected HER2 mutations were activating or deleterious, but not all were clonal. Updated outcome data, including overall survival, will be given at the time of presentation.
Conclusion: A much larger subset of patients with ER+/HER2- MBC have HER2 mutations detectable by ctDNA, but not by tissue, which highlights the need for blood-based biomarker monitoring for identification of actionable mutations, as well as the potential clinical utility in development of genotype driven trials for patients with HER2 mutant, ER+/HER2- MBC.

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Alexander Melamed, MD MPH, OB/GYN

Effect of adoption of neoadjuvant chemotherapy for advanced ovarian cancer on all-cause mortality

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Introduction: Ovarian cancer is the fourth leading cause of cancer death among women in the United States, and is usually diagnosed after it has metastasized within the peritoneal cavity. Although two randomized trials found equivalent overall survival and reduced surgical morbidity with neoadjuvant chemotherapy (NACT) followed by surgery compared with primary cytoreductive surgery, the use of NACT remains controversial in the United States. Despite the skepticism, use of NACT for stage IIIC and IV ovarian cancer has increased gradually in the United States. In particular, two regions increased the use of NACT by more than 25% between 2011 and 2012, providing an ideal natural experiment to assess the causal effect of increased utilization of NACT on survival in women with advanced epithelial ovarian cancer using a fuzzy regression discontinuity design.
Methods: Use of neoadjuvant chemotherapy for stage IIIC and IV ovarian cancer has increased gradually in the United States since 2007, but rates of adoption vary by region. Between 2011 and 2012, use of neoadjuvant chemotherapy increased by 27% in the New England and East South Central regions, but remained unchanged in three control regions (South Atlantic,

West North Central, and East North Central regions). Employing prospectively collected data from Commission on Cancer-accredited cancer programs in the United States, we used this discontinuity in treatment approach to assess the causal impact of neoadjuvant chemotherapy on all-cause mortality in a quasi-experimental fuzzy regression discontinuity design. Kaplan-Meier curves and proportional hazard models were estimated to compare mortality differences between rapidly-adopting regions and controls. We also conducted a cross-sectional analysis of the relationship between regional use of neoadjuvant chemotherapy and survival.

Results: We identified 1,156 women treated for advanced epithelial ovarian cancer during 2011 and 2012 in the two rapidly-adopting regions and 4,878 women in the three control regions. In the rapidly-adopting regions, patients treated in 2012 compared with 2011 had a mortality hazard ratio (HR) of 0.81 (95%CI=0.71-0.94) after adjusting for mortality time trends, while no difference was observed in control regions (HR=1.02, 95%CI=0.93-1.12). Compared with control regions, we observed larger declines in 90-day surgical mortality (7.0% to 4.0% versus 5.0 to 4.3%, p=0.01) and in the proportion of women not receiving surgery and chemotherapy (20.0% to 17.4% versus 19.0 to 19.5%, p=0.04) in rapidly adopting regions. Cross-sectional analysis confirmed that treatment in regions with greater use of neoadjuvant chemotherapy was associated was lower mortality (p=0.001).

Conclusion: Adoption of neoadjuvant chemotherapy for advanced epithelial ovarian cancer in New England and East South Central regions led to a reduction in mortality within three years after diagnosis.

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Victoria Melchert, Bachelor of Science, Medicine - MGH Cancer Center

Distinct Immune-Based Signatures in HPV-positive Versus HPV-negative Head and Neck Cancers

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Introduction: Head and neck squamous cell carcinoma (HNSCC) is one of the most common cancers worldwide and accounts for approximately 2% of all cancer deaths. Two distinct etiologies of this disease raise the possibility of differential treatment strategies: most HNSCCs are causally related to tobacco and alcohol use, whereby a smaller percentage (up to 25%) are caused by human papillomavirus (HPV) infection. While HPV-related HNSCC is generally associated with better prognosis, their incidence is increasing worldwide and there are few novel treatment options available, making them an underserved patient group. Evasion of the immune system is particularly relevant in this malignancy, but the underlying mechanisms of immune escape would likely be distinct for viral versus non-viral tumorigenic mechanisms. Therefore, the goal of our research was to identify discrete immune signatures in HPV-positive versus HPV-negative HNSCCs to identify specific biomarkers that could direct immune modulation strategies.

Methods: We developed a custom cancer-immune RNA expression panel on the Luminex platform to evaluate the tumor immune microenvironment across a number of targets simultaneously. Several biological functions were represented, including inflammation (*n*=71), immune cell phenotypes (*n*=34), immune cell functional status (*n*=47), immune cell trafficking (*n*=36), suppressive pathways (*n*=26), immune checkpoint pathways (*n*=33), and tumor neoantigen profile (*n*=17). A significant benefit to the assay is the use of branched DNA technology and a hybridization-based approach, which results in signal rather than target amplification, thereby reducing the introduction of bias from RNA isolation, cDNA synthesis, and PCR amplification that results in lower baseline "noise." This provides higher confidence in dissecting out minor immune cell signatures from a complex cancer tissue for further evaluation. Tissue homogenates were prepared from formalin-fixed, paraffin-embedded (FFPE) tissue from HPV-associated (*n*=14) and non-HPV-associated (*n*=22) HNSCCs. Data analysis was performed by normalizing the fluorescence intensity readings against five evaluated housekeeping genes. Relative RNA expression signals were compared across and within the two patient cohorts to examine the ability to detect differential immune-related biomarker signatures. Expression signatures of interest were used to direct multi-target immunofluorescence in order to gain perspective of the signature in the larger tumor microenvironment.

Results: Broad-based immunoprofiling demonstrated striking differences in immune-related gene expression signatures between the HPV-associated and non-HPV-associated HNSCC cohorts. HPV-positive cancers revealed an inflamed signature with a greater extent of T-cell infiltration, whereby a subset of HPV-negative cancers demonstrated very low levels of inflammation. Interestingly, the magnitude of CD8 signature was inversely proportional to IL-6 expression across the two HNSCC etiologies. A subset of the HPV-negative cohort displayed lower MHC Class I RNA expression and this was inversely correlated with IFN-gamma expression. The use of our immunprofiling panel together with multi-target

immunofluorescence revealed distinct immune checkpoint signatures involving PD-1, PDL-1, PDL-2 and TIM-3 that was associated with HPV-positive versus HPV-negative HNSCCs.
Conclusion: Our RNA expression approach when paired together with multi-target immunofluorescence has revealed cancer-immune signatures that are specific to viral-mediated versus non-viral mediated HNSCC. While immune exhaustion signatures were evident between both etiological groups, the differential underlying mechanisms would indicate very distinct targeting approaches with immune modulators.

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Ruoyu Miao, MD, Radiation Oncology

Radiation Associated and Neurofibromatosis Associated MPNST Have Worse Outcomes Than Spontaneous MPNST

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Introduction: In an IRB approved protocol, we reviewed the clinical characteristics and outcomes of patients treated for malignant peripheral nerve sheath tumor (MPNST) at our institution and sought to characterize the impact of association with clinicopathologic features and treatment modalities on clinical outcomes.
Methods: We identified 275 patients with MPNST treated at our institution between 1960 and 2015 and collected the clinical information. Overall survival (OS), local control (LC) and metastasis-free survival (MFS) were estimated using the Kaplan-Meier method. The multivariate Cox proportional hazards regression was used to analyze survival outcomes and risk variables.
Results: With a median follow-up of 43.2 mo (range: 0.5-464.3), the median OS was 68.2 mo (95% CI: 45.7-90.6). There were 134 men and 141 women with a median age of 41 y (range: 3-95). Patients were classified as having either radiation-associated MPNST (raMPNST, n=19), neurofibromatosis-associated MPNST (nfMPNST, n=75), or spontaneous MPNST (sMPNST, n=181). The median time to development of raMPNST from prior radiation was 15 y (range: 6-50). Prior diseases in patients developing raMPNST included Hodgkin disease (8), testicular cancer (4), Wilms disease (2), benign disease (2), lung cancer (1), nasopharyngeal cancer (1), and ALL (1) at a median age of 21 y (range: 1-53). Compared with sMPNST, nfMPNST occurred relatively early in age (median: 31 y in nfMPNST, 36 y in raMPNST, 46 y in sMPNST, $p<0.001$). The rate of metastatic disease on presentation was similar (10.5% raMPNST vs 10.7% nfMPNST vs 10.5% sMPNST). No significant difference was found in surgery or chemotherapy (p=NS), although fewer patients with raMAPNST received radiation therapy (52.6% raMPNST vs 80% nfMPNST vs 64.1% sMPNST, p=0.016). On univariate analysis, both raMPNST and nfMPNST showed worse OS (median: 16.2 mo, 35.5 mo vs 102.4 mo, $p<0.001$), LC (13.3 mo, 75.1 mo vs 223.9 mo, p=0.047), and MFS (14.8 mo, 42.6 mo vs median not reached, $p<0.001$) than sMPNST, although the differences between raMPNST and nfMPNST were not significant. On multivariate analysis, older age (HR=1.015, 95% CI: 1.006-1.025, p=0.002), raMPNST (HR=2.358, 95% CI: 1.310-4.243, p=0.004), nfMPNST (HR=1.942, 95% CI: 1.305-2.891, p=0.001), trunk (HR=1.739, 95% CI: 1.205-2.509, p=0.003), tumor size > 5 cm (HR=1.705, 95% CI: 1.119-2.599, p=0.013), positive lymph node (HR=3.204, 95% CI: 1.254-8.186, p=0.015), metastatic disease at diagnosis (HR=1.978, 95% CI: 1.220-3.206, p=0.006), and positive margin (HR=1.928, 95% CI: 1.327-2.799, p=0.001) were related with worse OS, whereas radiation therapy (HR=0.577, 95% CI: 0.405-0.822, p=0.002) and surgery (HR=0.264, 95% CI: 0.125-0.555, $p<0.001$) was associated with improved OS. Among the 246 patients without metastatic disease at diagnosis, nfMPNST (HR=2.100, 95% CI: 1.316-3.350, p=0.002), primary disease in head/neck (HR=2.004, 95% CI: 1.158-3.467, p=0.013) or trunk (HR=2.279, 95% CI: 1.391-3.736, p=0.001), and positive margin (HR=4.573, 95% CI: 2.807-7.452, $p<0.001$) were related with worse LC, whereas radiation therapy (HR=0.359, 95% CI: 0.231-0.558, $p<0.001$) was correlated with improved LC. raMPNST (HR=2.353, 95% CI: 1.131-4.897, p=0.022), nfMPNST (HR=2.090, 95% CI: 1.339-3.263, p=0.001), and tumor size > 5 cm (HR=2.518, 95% CI: 1.368-4.636, p=0.003) were correlated with worse MFS.
Conclusion: Both radiation-associated and neurofibromatosis-associated MPNSTs have poorer prognosis than spontaneous MPNSTs, and warrant further characterization to determine optimal treatment.

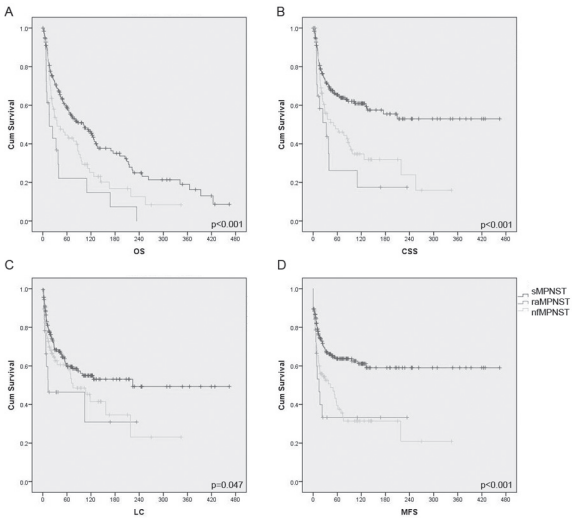

Fig 1. Kaplan-Meier curves of overall survival (A), cause-specific survival (B), local control (C) and metastasis-free survival (D).

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Alba Miranda-Ribera, PhD, Pediatrics

Zonulin Transgenic Mouse as a Model of Gut-Brain Axis Crosstalk Influencing Behavior

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Introduction: Recent studies have shown that the intestine has a relevant role in providing a dynamic barrier to regulate the trafficking of environmental antigens across the host mucosa and in controlling the balance between tolerance and immunity to non-self antigens. The integrity of the intestinal barrier appears to be a key element in preventing uncontrolled passage of antigens and the onset of immune responses. Increased intestinal permeability has been correlated to chronic inflammatory diseases, including autoimmune disorders. Further, neuroinflammation and a leaky blood brain barrier (BBB) have been associated with microbiota-driven increased intestinal permeability. Several studies point to a gut-brain connection associating an impaired intestinal barrier to neurological diseases involving neuroinflammation. Zonulin [human prehaptoglobin-(HP)-2] has been identified as the principal and so far, only, endogenous regulator of epithelial and endothelial tight junctions. **Aim:** Characterizing the zonulin transgenic mouse (Ztm) to understand whether it can be used as a model to study gut-brain axis dysfunctions leading to abnormal behavioral manifestations typical of neurobehavioral disorders such as ASD.
Methods: In our study, we used a zonulin transgenic mouse model expressing two copies of the zonulin gene [human prehaptoglobin-(HP)-2]. TJ proteins gene expression were evaluated by qPCR both at the intestinal and at the BBB level. Mice were also tested for repetitive behavior (marble burying), low anxiety activity (open field), and behavior in a mild anxiogenic setting (elevated zero maze).
Results: Zonulin transgenic mice had increased small intestinal permeability at baseline compared to wt (C57BL/6J) ($p<0.01$). These changes were associated with a downregulation of claudin 3 (CLDN-3), CLDN-15 and membrane palmitoylated protein 5 (MPP5). To test vascular brain permeability, we evaluated the expression level of major components of the brain endothelial tight junctions (CLDN-1, -3, -5, -12, occludin) along with known markers of neuroinflammation (TSPO, IBA-1) by qPCR. We did not observe any significant difference between wt and zonulin transgenic mice, suggesting an unaltered BBB gene expression profile, but we did observe an increased CLDN-5 protein expression (by western blot) in the cortex of the transgenic male mice. Our behavioral tests show differences between males and females, with transgenic females showing more repetitive behavior (marble burying), while transgenic males appeared less anxious (open field). When evaluated in a mild anxiety setting (elevated zero maze) zonulin transgenic mice appear to be more anxious than wt mice.
Conclusion: Conclusions: Our results suggest zonulin transgenic mice have an impaired gut epithelial barrier associated with increased intestinal zonulin gene expression levels and altered tight junction gene expression, compared to wt mice. Although we did not see changes in gene expression level of BBB components, we observed increased CLDN-5 in the cortex of transgenic mice, suggesting an altered BBB. When tested for behavior zonulin transgenic mice showed sex-dependent differences: females displayed more repetitive/obsessive behavior, while males were less anxious (in a low anxiety setting).

In a mild anxiety setting (elevated zero maze) transgenic mice showed a more anxious phenotype compared to wt mice. Combined, our data suggest that the zonulin transgenic mouse model could be a useful tool to study the gut-brain crosstalk in health and disease.

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Julian Mitton, MD, MPH, Medicine - General Internal Medicine

The association of a colorectal cancer screening patient navigation program with adherence to recommended follow-up surveillance colonoscopy.

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Introduction: Colorectal cancer (CRC) can be prevented using colonoscopy to detect early invasive disease and remove precursor lesions. Patients who have had a polypectomy are at higher risk for developing CRC and often require follow-up surveillance colonoscopy (FSC). Disparities in CRC screening and outcomes exist in minority and non-English speaking populations. Patient navigation (PN) has been shown to increase CRC screening colonoscopy rates in these populations, however less is known about the impact of PN on adherence to FSC. Our objective is to evaluate the impact of PN at time of initial screening colonoscopy on adherence to FSC.
Methods: We performed a retrospective matched-control cohort study in an urban academic primary care network. Patients 50-74 years old enrolled in a CRC screening PN program at a community health center who had an abnormal screening colonoscopy in 2010-2011 requiring FSC were matched by chart review in a 1:3 ratio by age, gender, race, language, and CRC risk category to patients at primary care practices without PN who also had abnormal screening colonoscopy requiring follow-up during the same time period. The main outcome is completion of FSC in the PN group compared to the matched controls. We conducted descriptive statistics and used a chi-square test for unadjusted comparison. We further analyzed FSC using multivariable logistic regression with adjustment for health insurance, education and prior number of annual clinic visits.
Results: There were 62 patients enrolled in CRC screening PN with 157 matched controls. Mean age was 60 years (SD 7.27), 40% were women, 58% non-Latino white, 59% spoke English, 11% required FSC in one year, 42% in 3 years, and 46% in 5 years. 72% of patients with PN at initial screening underwent a timely FSC compared to 71% in the non-PN matched control group (p=0.850). After full adjustment, patients with PN had similar odds of completing FSC (OR=0.99, CI 0.49-2.00) compared to those without PN.
Conclusion: In our study, nearly 30% of patients with abnormal screening colonoscopies did not complete recommended FSC. PN at initial screening colonoscopy did not appear to improve the odds of FSC. Future research should seek to better understand if PN at the recommended time of FSC, rather than only at time of screening colonoscopy, would improve adherence to FSC and equity in CRC outcomes. These results have implications for primary care practices seeking to improve access and adherence to follow-up surveillance colonoscopy, especially those serving minority and non-English speaking patients.

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Ramin Mohammadi, PHD Candidate, Medicine

Development of an Engagement Engine to Support Long Term Use of Fitness Trackers and Sustain Physical Activity

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Introduction: Sustained tracking of physical activity can lead to habitual exercise routines and decrease disease risk. However, many new users experience a sharp decrease in tracker use within months of initial use. Users stop using activity trackers for various reasons including losing interest and lack of support. Innovative, personalized approaches that increase continued use could lead to not only acceptance of tracking but also more regular engagement in exercise. Here, we discuss a multi-phased approach to developing an engagement engine to support long-term use of fitness trackers by adjusting a participant's step goal based on performance and engagement during the previous week and personalized text messaging. The objectives of this study are to first identify reasons for non-engagement with activity trackers and then build a machine learning algorithm to support continued use of activity trackers.
Methods: Overweight and obese participants (n=30) were recruited to use activity trackers to record their step counts every day for 9 weeks. Participants completed physical activity behavior-related questionnaires including Proschka's Stage of

Change, Barriers to Being Active and Behavioral Regulation of Exercise Questionnaire at 0 and 9 weeks. 158 variables generated from study questionnaires were analyzed to determine their appropriateness for inclusion in the algorithm. Highly correlated and near zero variance variables were eliminated which resulted in 87 variables. To determine the number of factors needed, eigenvalues were calculated and 19 factors were generated with eigenvalues greater than one, which encompassed 98% of the variance. Shannon entropy was used to generate a weekly value, calculated from participants' step counts, that served as an indicator of how likely a participant is to be engaged with their activity tracker. The19 factors combined with step data and a Shannon entropy value from the past 7 days served as the input to a neural network prediction model. 90% of available data was used as training set for the algorithm while the remaining 10% was used as a test set

Results: A neural network that predicts a participant's step goal based on their responses to study questionnaires, available step data and Shannon entropy value was developed. The machine learning algorithm's neural network was developed using the backpropagation method, two hidden layers, 20 nodes and learning rate equal to 0.001. Mean squared error of the model was 0.00125.

Conclusion: Artificial intelligence applied to physical activity data combined with behavioral data may be used to increase engagement with activity trackers. A follow-up prospective study is ongoing to determine the performance of the engagement algorithm.

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Kamyar Mollazadeh Moghaddam, Pharm.D., Emergency

A Novel Air-Oxygen Blender for An Ultra Low-Cost bubble-CPAP Kit

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Introduction: Respiratory distress is a major causes of neonatal death around the world. Limitations in delivering appropriate treatments make the morbidities and mortalities of respiratory distress more critical in low- and middle-income countries. Oxygen therapy is the most common treatment method to treat patients in respiratory distress, and at times is best delivered using a continuous positive airway pressure (CPAP) device. However, these devices are expensive and require electricity to drive the pump delivering the oxygen, making it difficult to provide treatment to remote areas around the world lacking in electric power and where the cost of the CPAP device is a major concern. Another issue is that the desired fraction of inspired oxygen (or FiO_2) is lower than 100% to prevent hyperoxia, which is associated with complications to lungs, eyes and brain for the infant receiving oxygen therapy. Therefore, a conventional CPAP device in an urban hospital setting is connected to a tank of compressed oxygen, which are ubiquitous, as well as a tank of compressed air, which are not as commonly available. The requirement of two gas tanks also make the device less portable. A bubble continuous positive airway pressure (bCPAP) device provides positive pressure by immersion of the expired air tube into a water bottle to provide the necessary back-pressure. This novel device does not require either an expensive electric power driven pump or electricity to drive the device. The flow of oxygen is provided by the compressed oxygen tank connected to it. This low cost device however suffers from lack of portability due to the need for both an oxygen and the less commonly available air tank. In this study, we sought to design and fabricate a compact ultra-low-cost air-oxygen blender for the bCPAP kits from a thermoplastic polymer.

Methods: A four-piece mold was designed using 3D CAD software (Solidworks Corp) to provide a 7 mm × 9 mm × 73mm rectangular shaped blender. The mold was machined from stainless steel and used in an injection molding machine (Medium machinery LLC) to inject polypropylene (Scientific Polymer Products) at 240°C. The fabricated part was slow cooled and removed from the mold to provide a finished part. Medical grade oxygen was used to measure the FiO_2 delivered by the blenders (n=6 for all experiments). The effect of the size of venturi nozzle on the FiO2 was evaluated by fabricating blenders with venturi nozzle of 0.5 mm, 0.6 mm, 0.7 mm, 0.8 mm, 0.9 mm, and 1mm. The cross-sectional area of the air entrainment window and the distance between venturi nozzle and the outlet orifice were also altered to determine their effect on FiO_2. The effect of oxygen flow rate and air temperature on FiO_2 were also examined in flow rate range of 0.25 to 15 L/min and a temperature range of 20°C to 50°C.

Results: The injection molding process provided low cost polypropylene blenders using a one-step procedure with tolerances that provided less than 5% standard deviation (n=6) in FIO2. It was shown that the blender can deliver a range of FiO2 percentage by changing the dimensions of the venturi nozzle. (Figure 1) FiO2 percentages varied from 34.2±1.2 to 53.0±0.7 for various venturi nozzle sizes of 0.5 mm to 1mm (Figure 2). Moreover, it was shown that the cross-sectional area of the air entrainment window and the distance between venturi nozzle and the outlet nozzle also varied the FiO2 percentage. A decrease in cross-sectional area increased the FiO2 content exponentially where 0 mm2 cross-sectional area make 100% FiO2 for all venturi nozzle sizes blenders. A decrease in the distance between inlet nozzle and exit orifice increased the FiO2

content linearly where the distance of 1mm make 61.0±3.6% FiO2 for the blender with venturi nozzle of 0.5 mm. These variables can enable the blender to be designed to generate a wide range of FiO2 percentage up to 100%. In addition, it was shown that the larger venturi nozzle sizes make the blenders more sensitive to the flow rate and the temperature alteration.
Conclusion: This study showed that a bubble CPAP can deliver a wide range of oxygen-enriched air using an ultra-low cost ambient air-oxygen blender. This compact, hand-held blender makes the bubble CPAP substantially more portable since it does not require connection to a tank of compressed air, which is not as easily available as a tank of compressed oxygen in resource-poor settings. We have already begun to employ bubble CPAP kits equipped with the ambient air-oxygen blender for trials in India and Kenya.

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Kylie N. Moore, Bachelor of Arts, Psychiatry

Hyperarousal and Habituation: Discrepancies in a Trauma-Exposed Population

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Introduction: Anxiety and traumatic-stress disorders are believed to be associated with impairments in emotional processing, learning, and memory that are accompanied by states of hyperarousal characterized by impaired habituation to aversive stimuli. One manifestation of such hyper-reactivity is an exaggerated startle response, often measured in laboratory settings with acoustic startle paradigms. Although hyperarousal is commonly associated with anxiety and traumatic-stress disorders, objective measurements of hyperarousal are rarely included as part of the diagnostic process – rather, subjective hyperarousal is evaluated based on self-report and general clinical observations. Accordingly, we sought to examine if subjective reports of hyperarousal were consistent with objective measurements of hyperarousal in a population of recently-trauma-exposed individuals.
Methods: Twenty-nine participants (ages 18-40, 12 males, 12 with current PTSD diagnosis) who had experienced a DSM-5 PTSD Criterion-A traumatic event in the past two years completed psychological interviews including the Clinician-Administered PTSD Scale (CAPS), the PTSD Checklist (PCL-5) and a self-report Hyperarousal Scale (HAS). Participants were assessed using an auditory loud tone paradigm while undergoing simultaneous recordings of heart rate (HR), skin conductance level, and electromyography (EMG). Skin conductance response (SCR), orbicularis oculi blink EMG, and HR accelleratory (HRA) responses to 100-102 dB loud tones were computed from these data. A composite hyperarousal index (CHI) was computed based on participants' scores on the CAPS hyperarousal sub-scale, the PCL-5 hyperarousal subscale, and the HAS. Mean responses and relative habituation to loud tones were calculated from these physiological data and regressed against subjective hyperarousal data (CAPS, PCL-5, HAS, CHI).
Results: There were robust positive correlations between CHI scores and total scores on the CAPS, PCL-5, and HAS ($r=.800$, $p<0.01$; $r=.821$, $p<0.01$, $r=.857$, $p<0.01$; respectively). However, although 9 high-CHI individuals also met criteria for current PTSD, there were no significant correlations between CHI scores and mean responses to loud tones in HRA, SCR, or blink-EMG data. We observed modest negative correlations between CHI scores and SCR habituation ($r=-.461$, $p<0.05$) and HR habituation ($r=-.454$, $p<0.05$) such that individuals who self-reported greater levels of hyperarousal paradoxically demonstrated more rapid SCR and HRA habituation to loud tones. CHI and EMG habituation were positively correlated ($r=.272$), indicating that individuals who self-reported greater levels of hyperarousal demonstrated slower habituation of eye-blink EMG to loud tones, but this trend did not reach significance ($p=.153$).
Conclusion: Our findings suggest that subjective measures of hyperarousal were not correlated with objective measures of hyperarousal. Further, subjective hyperarousal was inversely correlated with rate of habituation of SCR and HRA to the loud tones, such that a high-CHI score would be predictive of more rapid SCR and HRA habituation. Although these data are at variance with some, but not all, previous studies, the observed trends may be better explained after closer examination. Recent studies suggest that physiological hyper-reactivity in a population of individuals with PTSD was driven by patients with a single recent trauma exposure; individuals who experienced multiple qualifying traumatic events throughout their lives demonstrated blunted startle responses. Importantly, these differences were not reflected in self-report measures of fear. Our data, considered in the scope of these findings, suggest that disorder duration and history of trauma may impact reactivity such that cumulative traumatization and associated chronic stressors may ultimately impair and inhibit physiological responses to acute aversive stimuli. Accordingly, this eventual impairment of defensive reflex mechanisms may manifest in physiological, but not subjective, measures of hyperarousal. Future studies aim to investigate the role of trauma history and chronic stress as factors in the analysis of the defensive response profile of individuals along the spectrum of PTSD symptom severity.

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Elisabetta Morini, PhD, Center for Human Genetic Research (CHGR)

Increasing IKAP expression by mRNA splicing modification improves phenotype in a mouse model of familial dysautonomia

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Introduction: Familial dysautonomia (FD) is a recessive neurodegenerative disease caused by a splice mutation in the *IKBKAP* gene that leads to variable skipping of exon 20 and to a drastic reduction of IKAP protein levels in the nervous system. The clinical features of FD are all due to a striking progressive depletion of sensory and autonomic neurons. FD is an incurable disease and the available treatments are only supportive and far from optimal.
Methods: We have recently created a new phenotypic mouse model of FD, *TgFD9; Ikbkap*$^{\Delta 20/flox}$, in which we can manipulate the human *IKBKAP* splicing and assess the effect of increasing IKAP levels on the disease phenotype. This new mouse is truly a breakthrough in the field of FD and allowed us to initiate a preclinical trial of the splicing modifier, kinetin, to fully evaluate the benefit of modulating *IKBKAP* splicing on disease phenotype and to set the stage for clinical trials in FD patients. Kinetin was administered to the FD mouse beginning at birth. The day of delivery (P0), regular mouse chow was replaced with kinetin or control diet, and the dam, randomly assigned, continues to be fed with this diet until the time of weaning. At weaning, mice were genotyped and maintained in the same treatment groups.
Results: Daily oral administration of kinetin leads to significantly improved *IKBKAP* splicing and increased IKAP protein levels. Moreover, kinetin treatment ameliorates several disease phenotypes including spinal abnormalities and motor coordination. Our study demonstrates for the first time that by targeting the disease-specific splicing alteration it is possible to improve disease symptoms and represents an important step forward toward the development of a splicing modulation therapy for FD. Over the past four years, our laboratory worked on optimizing the potency and efficacy of kinetin to create a new class of splicing modulator compounds (SMCs) designed to promote exon inclusion. We are now collaborating with the pharmaceutical company PTC Therapeutics, Inc. to continue the improvement of these compounds with the goal of developing a treatment for FD.
Conclusion: These exciting results prove that splicing modulation has great therapeutic potential and serve as proof of concept for future efficacy studies of other more potent splicing modulator compounds that are in development.

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Jessica L. Mow, B.S., Athinoula A. Martinos Center for Biomedical Imaging

Time course of brain responses to intrusions into personal space

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Introduction: One type of non-verbal social communication, that appears to be altered in several neuropsychiatric conditions including autism and schizophrenia, is social spacing or "personal space", the distance that one prefers to maintain in relation to other individuals (Nechkamin et al., 2003; Deus et al., 2006; Rudie et al., 2012). We and others have found that patients with schizophrenia show an enlarged or less flexible personal space boundary (Holt et al., 2014; Deus et al., 2006; Duke and Mullens, 1973), and that these abnormalities in social spacing are linked to the presence or severity of negative symptoms (e.g., impairments in motivation and social drive) (Nechamkin et al., 2003; Park et al., 2009). Thus, abnormalities in personal space may represent a promising quantitative biomarker of negative symptoms in schizophrenia. Such a biomarker is greatly needed for use in clinical trials of potential agents for the treatment of negative symptoms. Although many of the psychological features of personal space have been well-studied (Hayduk,1983), the neurobiological mechanisms governing regulation of personal space are less well-understood. We recently conducted an functional magnetic resonance imaging (fMRI) study which revealed that a parietofrontal cortical network that was previously shown to be involved in monitoring the space near the body in primates (Colby et al., 1993; Graziano et al., 2006) selectively responds to stimuli that "loom" towards the body and cross into personal space (Holt et al., 2014). Moreover, looming responses only occurred in response to faces, but not to cars or simple spheres. To better understand the functioning of this neural system, we recently conducted a study using the same experimental paradigm as in Holt et al, 2014 in 131 young adults. We sought to determine exactly when the regions that respond to looming stimuli exhibit differential responses to personal space intrusions. Do these responses occur

in anticipation of personal space intrusions (beginning when the stimuli are beginning to approach, but are still far from, the participant), or are these responses signaling that there is an object within personal space?
Methods: Analyses were conducted on fMRI data collected from 131 participants who were recruited from Boston-area college campuses during mental health screening events. Data consisted of fMRI scans during which subjects viewed 1) computer generated, realistic appearing faces with neutral emotional expressions and 2) photographs of cars. The stimuli were presented individually, and appeared to either approach or withdraw from the subject at approximately the speed of walking. Each stimulus presentation lasted for 16 seconds with a TR of 2000ms, providing 8 time points per stimulus presentation. Using the fMRI data analysis stream of FreeSurfer, signal was extracted from 10 regions of interest (ROI), defined based on the clusters showing significant activation with the contrast Face Approach vs. Face Withdrawal (whole brain cluster corrected at $p < .05$ using a Monte Carlo simulation, 10,000 iterations). Our hypothesis-testing focused on the region that showed the largest looming effect in the Holt et al, 2014 study, the dorsal intraparietal sulcus (DIPS), which was comprised of three ROIs: two in the right and one in the left hemisphere. For each ROI, average raw signal values were extracted for each of 10 time points for each condition of interest (Face Approach, Face Withdrawal). The final analyses were conducted using data from 120 subjects; eleven subjects were excluded from the original cohort of 131 due to poor data quality. An average, typical personal space boundary was calculated using personal space data collected in 14 independent healthy subjects. The average time when this boundary is crossed during the experimental paradigm (15.76 seconds following stimulus onset) was then estimated. A 2 x 10 repeated measures ANOVA was conducted with the fMRI data, with condition (Faces Approach, Faces Withdrawal) and time (10 TRs) as factors.
Results: ANOVAs revealed a significant main effect of time and of condition, and a significant time by condition interaction, for all three DIPS ROIs (all ps <.001). Plots of the time course of each ROI revealed two looming (Approach > Withdrawal) response peaks: one occurred early and a second began just before the personal space boundary was reached. Post-hoc paired t-tests confirmed this pattern, revealing significantly greater responses to the Approach compared to the Withdrawal condition at 2-10 seconds, and at 14-20 seconds, following stimulus onset (all ps < .001) for the three DIPS ROIs.
Conclusion: An analysis of the time course of brain responses to personal space intrusions revealed two components of this response, one that occurs early and one that is proximal to the personal space intrusion and is maintained while the stimulus remains within personal space. The first component may reflect an anticipatory, orienting response to an object that is suddenly recognized to be on a collision course with the body, whereas the second component may correspond to a signal that the personal space boundary is about to be or has been breached. Additional experiments that vary attention to the stimuli and personal space boundaries across conditions will further test these interpretations. These results will also inform ongoing studies of patient populations that examine whether abnormalities in personal space in these groups are linked to changes in the functioning of this personal-space-monitoring network.

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Matthias Mueller, PhD, Dermatology

Combined treatment of X-rays with UVC emitting nanoparticles results in a synergistic decrease in cell viability

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Introduction: Radiation therapy is the gold standard treatment for inoperable malignant tumors. However, irradiation of normal tissue can lead to deleterious side effects such as fibrosis. To increase the efficiency of radiation therapy, we propose combining traditional X-ray treatment with tumor-localized UVC emitting $LuPO_4:Pr^{3+}$ nanoparticles. Using the combined treatment, X-rays are converted by nanoparticles into UVC radiation inside the tumor. UVC damages the DNA directly via an oxygen-independent mechanism which could improve treatment efficacy within hypoxic tumor areas. In addition, due to the limited penetration depth of UVC radiation, only tumor tissue is affected by local UVC exposure, while normal surrounding tissue is spared.
Methods: The effect of generated UVC emission under X-ray irradiation was tested on human foreskin fibroblasts (HFF1) pretreated with nanoparticles. For that reason, the nanoparticles were dispersed in medium and precipitated on the cells. Subsequently, the cells were irradiated with an X-ray dose of 2 Gy. Viability of the cells was measured 48 h and surviving fraction 14 days after combined treatment using the MTT- and colony formation assay, respectively.
Results: Both assays illustrated an increased loss of cell viability following combined treatment. While the MTT-assay revealed a minor effect, a significant increased loss in surviving fraction up to 80 % was demonstrated by the colony formation assay. The data of the colony formation assay revealed that the combined treatment with UVC emitting nanoparticles followed by X-ray irradiation with 2 Gy, results in a reduction of surviving fraction which is equivalent to an X-ray dose of 4 Gy alone.

Conclusion: Our study suggests that combined treatment is more efficient for cell killing. This might allow a reduction in total administered radiation dose to reduce side effects while maintaining treatment efficacy. Further research is necessary to confirm these results, in addition to optimizing efficiency, minimizing non-specific toxicity of the nanoparticles and investigating the uptake of the particles by the tumor. This could be achieved by changing the size, shape, and composition of the particles, as well as coating them with biocompatible materials.

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Meredith P. Murphy, BS, Neurology

Cardioembolic Risk and Recovery after Anticoagulation-Related Intracerebral Hemorrhage

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Introduction: Oral Anticoagulation Treatment (OAT) resumption remains a key unresolved question in Intracerebral Hemorrhage (ICH) care because patients and clinicians must weigh the increased risk of recurrent bleeding against the beneficial protection from thromboembolic events. Previous studies found OAT resumption is associated with decreased mortality risk, decreased ischemic stroke risk, and improved functional outcome at one year post-ICH. However, we believe that OAT may also be decreasing the incidence of asymptomatic (i.e. subclinical) ischemic strokes as an additional mechanism linking OAT resumption to favorable outcome post-ICH. We sought to use individual CHA_2DS_2-VASc scores (an established measure of cardioembolic risk) to model the burden of risk for cardioembolic events. Moreover, prior studies only focus on outcome at one year post-ICH, but have not evaluated recovery. In order to assess post-ICH recovery, we opted to exclude fatal cases as well as cases of recurrent ICH and subsequent symptomatic ischemic stroke. Therefore, we sought to investigate whether cardioembolic risk worsens recovery after OAT-ICH, even in the absence of recurrent strokes, and whether OAT resumption mitigates the impact of cardioembolic risk on post-ICH recovery.
Methods: We conducted joint analyses of three observational studies: 1) the multi-center RETRACE study conducted in Germany from 2006 to 2010 (n = 317); 2) a longitudinal ICH study (MGH-ICH) conducted in Boston, USA from 1994 and ongoing (n = 166); 3) the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study conducted from 2011 to 2015 (n = 131). Eligible participants were 1) diagnosed with primary ICH (confirmed on CT scan) at a participating center, 2) age 18 years or older at time of ICH, 3) without history of prior ICH (before the index event at enrollment); 4) on active oral anticoagulation therapy (OAT) for prevention of cardioembolic stroke due to previously diagnosed non-valvular atrial fibrillation at time of ICH; 5) alive and eligible for potential OAT resumption (i.e. with care not focused on comfort measures only) at time of discharge from inpatient hospital stay for index ICH; 6) alive and available for follow-up at one year; 7) not diagnosed with recurrent ICH or ischemic stroke at one year follow-up. We determined the associations between cardioembolic risk (defined by CHA_2DS_2-VASc score), OAT resumption, and functional recovery after ICH (defined as ≥ 1 point decrease in modified Rankin Scale (mRS) score at one year post-ICH vs. at discharge). For statistical analyses, we initially conducted separate univariable and multivariable analyses for the RETRACE, MGH-ICH and ERICH studies. Results from multivariable regression analyses in each individual study were then meta-analyzed using a conservative inverse variance-based random effects pooling method.
Results: CHA_2DS_2-VASc score was associated with decreased likelihood of functional recovery at 1 year after ICH (Odds Ratio [OR] = 0.73 per 1 point increase, 95% Confidence Interval [CI] = 0.62 – 0.88, $p < 0.001$). OAT resumption was independently associated with higher likelihood of recovery, regardless of CHA_2DS_2-VASc score (OR = 2.93, 95% CI = 1.25 - 4.61, p = 0.001). Interaction analyses (Figure 1) clarified that subjects with higher CHA_2DS_2-VASc score benefited more from OAT resumption in terms of functional recovery (OR = 1.69 for improved recovery, CI = 1.20 – 2.38, p = 0.003).
Conclusion: Increasing cardioembolic risk was associated with decreased likelihood of functional recovery following ICH. This effect was mitigated by OAT resumption, with the greatest benefit seen in subjects at highest cardioembolic risk. These findings strongly support including recovery metrics in future studies of OAT resumption after primary ICH.

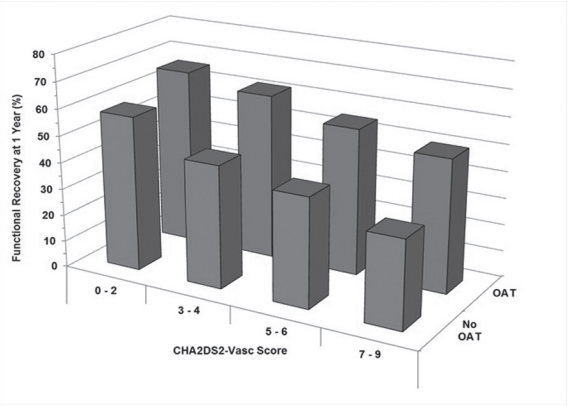

Figure 1. CHA^2DS^2-VASc Score, Oral Anticoagulation Resumption and Functional Recovery after Intracerebral Hemorrhage

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Konstantinos S. Mylonas, M.D., Surgery - Pediatric

Near-Elimination of Opioid Use in Inguinal Herniorrhaphy Using a Systematic, Patient-Centered and Procedure-Specific Approach to Perioperative Pain Management

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Introduction: A better understanding of the analgesia needs of patients who undergo common surgical procedures is necessary as we address the growing opioid public health crisis in the United States. The aim of this study was to evaluate our comprehensive approach to perioperative analgesia to determine whether we can effectively decrease postoperative opioid use in patients undergoing inguinal herniorrhaphy.

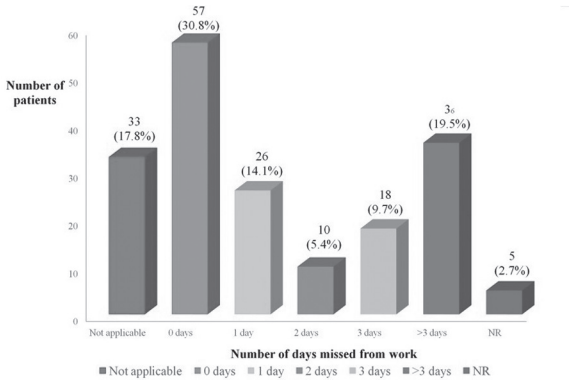
Methods: A prospective, observational study was conducted between October 1, 2015 and September 30, 2016 in a single-surgeon, high-volume, inguinal hernia practice. Adult patients undergoing inguinal herniorrhaphy under local anesthesia and intravenous sedation were invited to participate. Although all patients were prescribed ten opioid analgesic tablets, they were counseled to reserve opioids for pain not controlled by non-opioid analgesics. Their experience was captured by completing a questionnaire 2-3 weeks after surgery at their postoperative visit.

Results: A total of 185 patients were surveyed. The majority of the participants were males (177, 95.7%), 60 years of age or older (96, 51.9%). 159 of 185 patients (85.9%) reported using four or less opioid tablets. 110 of 185 patients (59.5%) reported that they used no opioid analgesics postoperatively. None of the patients were taking opioids within seven days of their post-operative appointment. 111 of 147 (75.5%) patients who were employed reported missing three or less work days and 57 of 111 of these patients (51.4%) missed no work at all. Patients who took no opioid analgesics experienced significantly less maximum ($p<0.001$) and persistent groin pain ($p= 0.037$). Pain interfered significantly less with daily activities ($p=0.012$) and leisure activities ($p=0.018$) for patients who did not use opioids.

Conclusion: A comprehensive, patient-centered and procedure-specific approach to perioperative pain management following inguinal herniorrhaphy resulted in the near elimination of opioid use. The majority of patients did not require any opioid analgesics and most of those who did used less than five tablets. These findings may be true for other commonly performed surgical procedures. Therefore, patient-centered, procedure specific opioid administration strategies (PSOAS) may be warranted.

Post-operative pain and use of opioid analgesics

Use of opioid analgesics for pain control after surgery (%)	
Yes	40
No	59.5
Number of opioid tablets that patients used after surgery (%)	
1	6.5
2 to 4	20
5 to 8	6.5
9 to 12	6.5
More than 12	0.5
Use of opioid analgesics within 7 days of the 2-3 week post-operative appointment (%)	
Yes	0
No	98.9
Average pain (%)	
0	39.5
2	40.5
4	17.8
6	1.6
8	0.5
Worst pain (%)	
0	10.8
2	22.7
4	23.2
6	26.5
8	13
10	3.8
Pain at the 2-3 week post-operative appointment (%)	
0	79.5
2	17.8
4	2.7



Days missed from work

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Khawaja S. Nasir, BDS, MSc, Oral and Maxillofacial Surgery

Effectiveness, safety, and predictors of response to botulinum toxin type A in refractory masticatory myalgia: A retrospective study

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Introduction: Temporomandibular disorders (TMD) are defined as a subgroup of craniofacial musculoskeletal and neuromuscular disorders that involve the temporomandibular joints (TMJ), the masticatory muscles, and the associated head and neck tissues. Masticatory muscle pain disorders are defined as painful disorders of muscle origin affected by jaw movements, function, or parafunction, and there is replication of this pain with provocation testing. Masticatory muscle pain disorders respond well to conservative therapy, however, in some patients the pain becomes refractory. Botulinum toxin type A (BoT-A) is a subtype of a potent presynaptic neurotoxin produced by Clostridium botulinum. It blocks the calcium ion-mediated release of acetylcholine at the neuromuscular junction. Independent of the neuromuscular effects, BoT-A has been suggested to have analgesic properties. It has been shown to be an effective modality in the management of refractory headache disorders and trigeminal and post-herpetic neuralgias. Conversely, there are conflicting reports in the literature regarding the efficacy of BoT-A therapy for management of refractory masticatory muscle pain. The aim of this investigation is to determine the efficacy and safety of BoT - A therapy in refractory masticatory muscle pain and, in addition, to identify demographic, diagnostic, and therapeutic characteristics that would predict the clinical outcome of BoT – A therapy.
Methods: This is a retrospective chart-review of patients that underwent at least 2 injection cycles of 100 units (U) of BoT-A for refractory masticatory myalgia in the department of Oral and Maxillofacial Surgery, Massachusetts General Hospital between May 2012 and June 2016. Information regarding demographic, diagnostic, and therapeutic characteristics was extracted and analyzed. The diagnosis of refractory masticatory myalgia was made if the patient had a diagnosis of masticatory myalgia (i.e., a positive history for presence of pain in the masticatory muscles and modification of that pain with jaw functional and parafunctional activity, clinical evidence and replication of pain in the masticatory muscles, pain modifies with palpation or during passive or active range of motion), for at least 12 months, and failure of at least 6 months of conservative therapy (e.g., patient education, behavioral management, physical therapy, occlusal orthotic device, and pharmacotherapy) to reduce the baseline pain of the patient by 50%. All adult males and females that had undergone at least 2 injection cycles of 100 U BoT – A, with an interval of at least 12 weeks in between, were included in the investigation. Patients with a concurrent diagnosis of post-surgical trigeminal neuropathy, were excluded. If participants had experienced relief of ≥75%, it was considered "*significant relief*"; if it was between >25% - <75% it was considered "*moderate relief*"; and if it was ≤25%, it was rated "*no or minimal relief*". Chi-Square test was used for analysis between independent and dependent variables. Forward step-wise type logistic regression analysis was conducted to determine the predictors of outcome.
Results: A total of 189 charts were identified and reviewed. One hundred and sixteen participants that underwent at least 2 injection cycles of 100 U BoT – A, with an interval of at least 12 weeks in between, were included in the present investigation. Among 116 participants, 30.6% reported significant relief in pain for a mean period of 10.1 weeks. A total of 16.4%

participants reported at least one adverse effect, and reduction in the size of masticatory muscles was the most commonly reported side effect. The effectiveness of the BoT-A therapy was found to be statistically associated with the presence of muscle hypertrophy (p=0. 004), range of motion (p=0. 02), concurrent use of opioid analgesics (p=0.003), and local anesthetic trigger point injections (p=0.003). Logistic regression analyses suggested that the presence of muscle hypertrophy and occurrence of adverse effects were predictors of positive outcome. On the contrary, concurrent use of opioid analgesics was found to be a predictor for no or minimal relief.

Conclusion: BoT-A therapy provides significant relief for approximately one-third of patients with refractory masticatory muscle pain. Therapy is associated with a mild risk of adverse effect. Presence of muscle hypertrophy, occurrence of an adverse effect and concurrent use of opioid analgesics were found to be predictors of outcome response.

Table 1

Study Characteristics	Category	Descriptive Statistic
Age (years)		45.35 ± 14.07
Body Mass Index		25.02 ± 5.29
Gender	Female	99 (85.3 %)
	Male	17 (14.7 %)
Pain Location	Bilateral	90 (77.6 %)
Muscle Hypertrophy		21 (21.2 %)
Range of Motion (mm)	≥ 40	70 (60.3 %)
Muscle Tightness		39 (36.4 %)
Parafunctional behavior		71 (70.3 %)
Morning Symptoms		23 (30.7 %)
Initial Pain Score		5.22 ± 2.07
TMJ Arthralgia		87 (75.7 %)
Disc Displacement with Reduction		34 (29.8 %)
Disc Displacement without Reduction		19 (16.7 %)
Degenerative Joint Disease		35 (30.2 %)
Chronicity (years)	1 – < 5	29 (27.1 %)
	5 - < 10	37 (34.6 %)
	≥ 10	41 (38.3 %)
Chronic Headaches		62 (53.4 %)
Chronic Neck Pain		69 (59.5 %)
Chronic Body Pain		44 (37.9 %)
History of Psychological Illness		39 (36.1 %)

Summary of demographic and diagnostic characteristics of the study population

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Khawaja S. Nasir, BDS, MS, Oral and Maxillofacial Surgery

Sleep quality and its relationship with pharmacotherapy and chronic orofacial pain

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Introduction: Orofacial pain and temporomandibular disorders (TMD) are often sources of chronic pain that can alter sleep patterns and lead to co-morbid sleep disorders. Evidence has shown an association between chronic pain, psychological disorders and sleep disorders, however there is no significant data assessing the relationship between pharmacotherapy for chronic orofacial pain disorders, particularly chronic opioid therapy and its effects on sleep. Thus, the aims of this study were 1) to evaluate the sleep quality (SQ) in patients with chronic orofacial pain; 2) to assess the association of SQ and pain levels in patients with chronic orofacial pain; and 3) to evaluate the association between SQ and pharmacotherapy for chronic orofacial pain, particularly opioid therapy.

Methods: The Pittsburgh Sleep Quality Index (PSQI) was used to measure SQ in a sample of 74 subjects diagnosed with chronic orofacial pain conditions. All the subjects were adults (age 18-85) recruited at the Department of Oral and Maxillofacial surgery at Massachusetts General Hospital. Medical charts were reviewed to extract information regarding the participants' demographic data, age, body mass index (BMI), duration of symptoms, pain level, and differential diagnosis. In addition, concurrent use of pharmacological agents such as opioid analgesic medications, non-steroidal anti-inflammatories, muscle relaxants, triptans, hypnotic and neuropathic agents (e.g., anticonvulsants, benzodiazepines, gabapentinoids, and tricyclic anti-depressants), irrespective of indication for use, was identified. Descriptive analysis was conducted and statistical analyses were performed using Pearson correlation coefficient and one-way ANOVA.

Results: Among the 74 participants, 63 (85.1 %) were females. The average age of the sample was 47.07 ± 14.81 years and mean body mass index (BMI) was 24.13 ± 7.83. Based on the differential diagnosis, 58 (78.3%) subjects presented with temporomandibular disorders; 10 (13.5%) with painful post-traumatic trigeminal neuropathy; 3 (4.1%) with burning mouth syndrome; and 3 (4.1%) with trigeminal neuralgia. The average of duration of symptoms was 52.1 ± 75.02 months and the average of pain level was 5.27 ± 2.17 among all the subjects. In addition, 61 (82.43%) subjects presented PSQI of 5 or greater, and 13 (17.57%) presented PSQI of less than 4. There was a positive and moderate correlation between level of pain and PSQI ($r = 0.5139$, $p < .0001$). In total, 72.9% (n=54) of the patients with chronic orofacial pain were utilizing at least one pharmacological agent for pain management. The PSQI was considerably higher in the subjects utilizing 2 or pain

medicines, than in the subjects who were not utilizing any pharmacological agent ($p < .01$). Further, subjects on concomitant opioid therapy (n=13) presented poor sleep quality (PSQI = 12.15), than subjects who were not on opioid therapy (PSQI = 9.49) and subjects who were not utilizing any pain medicines (PSQI = 6.70, $p < .01$).
Conclusion: Sleep quality is impaired in subjects with chronic orofacial pain, and even more on those with higher pain levels or utilizing opioid therapy.

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Pradeep Natarajan, MD, MMSc, Medicine - Cardiology

Human knockouts and phenotypic analysis in a cohort with a high rate of consanguinity

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Introduction: Gene disruption in model organisms followed by phenotypic analysis has been a fruitful approach to understand gene function; here, we extend this concept to the human organism, leveraging naturally-occurring null mutations, consanguinity, and extensive biochemical phenotyping.
Methods: Null mutations (i.e., nonsense, frameshift, or splice-site mutations) are very rare in the general population but consanguineous unions are more likely to result in offspring who carry homozygous null mutations. We sequenced the protein-coding regions of 10,503 adults living in Pakistan, where consanguinity rates are amongst the highest in the world, to find participants knocked out for genes. We phenotyped all participants for >200 cardiometabolic traits and tested whether knockouts differed from wild-type across all phenotypes. For a single gene, we performed genotype-based recall of homozygous nulls and wild-type participants followed by provocative physiologic testing.
Results: We studied adult participants in the Pakistan Risk of Myocardial Infarction Study (PROMIS), designed to understand the determinants of cardiometabolic disease in South Asians. In PROMIS, 38% of participants reported that their parents were cousins. Whole exome sequencing of 10,503 participants, yielded 49,138 null mutations in 13,074 genes. The median excess homozygosity, derived by the inbreeding coefficient, was 1.6% of the genome compared to 0.4% in outbred populations ($P < 2x10^{-16}$) (Figure 1). Across all 10,503 PROMIS participants, both copies of 1,317 genes were disrupted by null mutations. About 1 in 5 sequenced participants (1,843) was a knockout. Simulations using the excess observed homozygosity suggest that with the sequencing of ~200,000 Pakistanis, we can expect about 8,000 genes to be completed disrupted, six-times larger than anticipated in outbred populations. In a screen across >200 cardiometabolic traits, homozygosity for null mutations at *PLAG27* was associated with absent enzymatic activity of lipoprotein-associated phospholipase A2; at *CYP2F1*, with higher plasma interleukin-8 concentrations; at *TREH*, with lower concentrations of apoB-containing lipoprotein subfractions; at either *A3GALT2* or *NRG4*, with markedly reduced plasma insulin C-peptide concentrations; and at *SLC9A3R1*, with mediators of calcium and phosphate signaling. *APOC3* heterozygous nulls were recently associated with reduced triglyceride concentrations and risk for coronary heart disease. We now describe the world's first *APOC3* homozygous null carriers whose phenotypes included: biochemical apolipoprotein C-III absence ($P=5x10^{-24}$); substantial fasting triglyceride reduction (-61.7%, $P=4x10^{-4}$) and HDL cholesterol increase (+28.1mg/dL, $P=6x10^{-9}$) (Figure 2). We recruited one *APOC3* null homozygote and his first-degree relatives for deeper phenoytping. We performed an oral fat tolerance test on knockouts and wild-type participants from this family to find that knockouts had significantly lower post-prandial rise in plasma triglycerides (area-under-the-curve 468.3mg/dL*6h vs 1267.7mg/dL*6h; $P=1.0x10^{-4}$).
Conclusion: Homozygous disruption of ~1,300 genes is tolerated in humans, and for several, we establish phenotypic consequences. Our work lays the foundation for a comprehensive project to understand gene function by studying human knockouts.

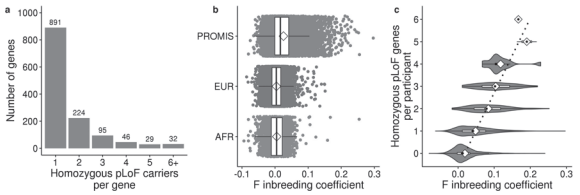

Fig 1. Homozygous pLoF burden in PROMIS is driven by excess autozygosity.

a, Most genes are observed in the homozygous pLoF state in only single individuals. **b.** The distribution of F inbreeding coefficient of PROMIS participants is compared to those of outbred samples of African (AFR) and European (EUR) ancestry. **c**, The burden of homozygous pLoF genes per individual is correlated with coefficient of inbreeding.

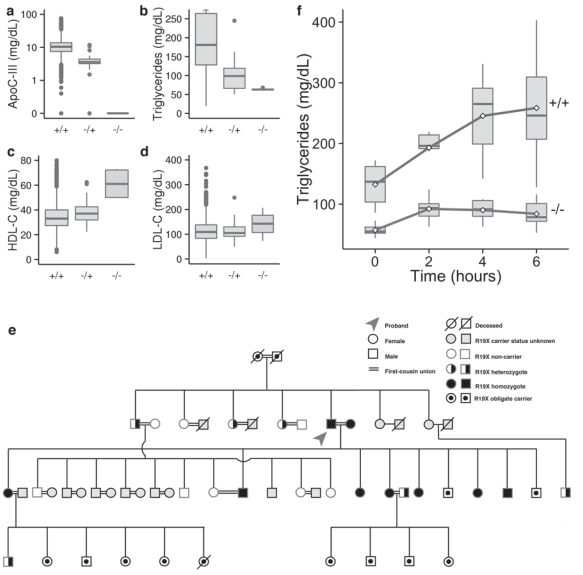

Fig 2. *APOC3* pLoF homozygotes have diminished fasting triglycerides and blunted post-prandial lipemia.

a.-d. *APOC3* pLoF genotype status, apolipoprotein C-III, triglycerides, HDL cholesterol and LDL cholesterol distributions among all sequenced participants. Apolipoprotein C-III concentration is displayed on a logarithmic base 10 scale. **e.** A proband with *APOC3* pLoF homozygote genotype as well as several family members were recalled for provocative phenotyping. Surprisingly, the spouse of the proband was also a pLoF homozygote, leading to nine obligate homozygote children. Given the extensive number of first-degree unions, the pedigree is simplified for clarity. **f.** *APOC3* p.Arg19Ter homozygotes and non-carriers within the same family were challenged with a 50 g/m^2 fat feeding. Homozygotes had lower baseline triglyceride concentrations and displayed marked blunting of post-prandial rise in plasma triglycerides.

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Maya Nauphal, BA, Psychiatry

ADHD and Emotion Dysregulation: Shared and Specific Clinical Features

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Introduction: ADHD has been conceptualized as a disorder of impaired self-regulation in attention, behavior, and more recently emotions. Emotion regulation deficits (i.e. emotion dysregulation) are prevalent among youth with ADHD and contribute to significant functional impairment and predict poor clinical outcomes (Shaw et al., 2014). Further, difficulties in emotion regulation are posited to play a significant role in the development of co-morbid psychiatric conditions among youth with ADHD (De Pauw & Mervielde, 2010). Indeed, previous research has demonstrated high rates of co-morbidity among individuals with ADHD with diagnoses of mood and anxiety disorders, oppositional defiant disorder, and conduct disorders (Steinberg & Drabick, 2015). Although research suggests that different emotion regulation profiles manifest in youth with ADHD, it remains unclear how these different profiles match onto or predict different co-morbid conditions (Steinberg & Drabick, 2015). As a first step, we aim to examine whether there are shared or unique profiles of emotion dysregulation in co-morbid conditions associated with ADHD in adolescence.

Methods: Participants included 59 adolescents between 12-18 years old diagnosed with ADHD (M_{age} = 28.8% Female, 57.6% Caucasian). Adolescents completed the Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004) to measure several features of emotion dysregulation (Table 1). The adolescent's parent completed the Child Behavioral Checklist (CBCL; Archenbach & Rescorla, 2001), a commonly used measure of psychiatric symptoms. In addition, both adolescents and their parents completed a semi-structured diagnostic interview (K-SADS-E; Orvaschel, 1995). To maintain fidelity, we used the interviewer's summary ratings based on 'best-estimate' clinical judgment from interviewing both parent and child. The K-SADS-E diagnostic interviews have good inter-rater and retest reliability (Orvaschel, 1995). To examine the shared or specific clinical features of emotion dysregulation we examined the association between emotion dysregulation with parent reported symptoms and diagnostic profiles.

Results: All participants met criteria for ADHD. The majority of the youth were currently prescribed stimulant medication (80%) and almost all of these youth had a history of treatment with medication and/or therapy for ADHD (95%). In addition, 33.3% of participants (N=19) met criteria for Major Depressive Disorder (MDD), 54.4% (N=31) met criteria for an anxiety

disorder (i.e. social phobia or GAD), and 35.7% (N=20) met criteria for Oppositional Defiant Disorder (ODD). First, we examined the association between emotion dysregulation and psychiatric symptoms. Broadly, internalizing symptoms were significantly correlated with all aspects of emotion dysregulation including non-acceptance of emotions (r=.274, p<.036), difficulties engaging in goal-directed behaviors when experiencing negative emotions (r=.274, p<.036), impulsive control difficulties (r=.413, p<.001), limited access to emotion regulation strategies (r=.312, p<.01) and lack of emotional clarity (r=.293, p<.05). Externalizing symptoms were only significantly correlated with impulse control difficulties, such that they have difficulties remaining in control of their behavior when experiencing negative emotions (r=.4, p<.01) and lack of emotional clarity (r=.322, p<.05). More specifically, symptoms of anxiety were significantly correlated with non-acceptance of emotions (r=.292, p<.05), impulse control difficulties (r=.425, p<.001), limited access to emotion regulation strategies (r=.312, p<.05) and lack of emotional clarity (r=.324, p<.05). Symptoms of depression were significantly correlated with difficulties engaging in goal-directed behaviors (r=.467, p<.001), impulse control difficulties (r=.406, p<.001), and limited access to emotion regulation strategies (r=.320, p<.05). Aggressive behaviors were significantly correlated with impulse control problems (r=.454, p<.001), limited access to emotion regulation strategies (r=.343, p<.01), and lack of emotional clarity (r=.428, p<.001). Second, we examined the association between emotion dysregulatoin and co-morbid diagnoses. Participants who met criteria for MDD reported significantly higher levels of non-acceptance of their emotional experience (t= -2.292, p<.05) and having a limited access to emotion regulation strategies (t= -2.063, p<.05). Participants who met criteria for ODD reported significantly higher levels of difficulty remaining in control of one's behaviors when experiencing negative emotions (t= -3.114, p<.01). Participants who met criteria for an anxiety disorder did not differ significantly from other co-morbid groups on any measures of emotion dysregulation.

Conclusion: This is the first study to our knowledge to assess whether emotion dysregulation is associated with unique or shared profiles in a sample of adolescents with ADHD. Our findings support the existence of different emotion dysregulation profiles across co-morbid conditions in youth with ADHD. Specifically, the presence of internalizing symptoms was broadly associated with many forms of emotion dysregulation and comorbid MDD presented with difficulties in acceptance of one's emotions and having a limited access to strategies of regulation. In contrast externalizing symptoms and ODD were more specifically associated with problems with remaining in control of oneself when experiencing negative emotions and having a poor understanding of their emotional experience (emotional clarity). These unique profiles point to the multifinality of ADHD presentations, such that a disorder diagnosed in childhood can manifest into different outcomes. Indeed, these emotion regulation profiles may have specific intervention strategies indicating that youth with ADHD who present differently may benefit from a more personalized approach to prevent the onset of further psychiatric outcomes and circumvent related functional impairments.

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Kamila Naxerova, PhD, Radiation Oncology

Origins of lymphatic and distant metastases in human colorectal cancer

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Introduction: The spread of cancer cells from the primary tumor to regional lymph nodes is one of the most important factors predicting survival in patients with epithelial cancers. Since lymph node metastasis is correlated with spread to vital organs, the prevailing view is that affected lymph nodes may give rise to distant metastases. The concept of such a sequential progression, in which the primary tumor seeds lymph node metastases, which in turn seed distant metastases, provides a mechanistic basis for the TNM staging system. A corollary of this model is that surgical resection of positive lymph nodes will reduce recurrence rates, but a number of clinical trials have shown that lymph node removal does not always improve patient survival. These findings have inspired the alternative view that lymph node metastases do not give rise to distant metastases and suggest that treatment strategies may need to be re-evaluated. Given its potential impact on patient care, a better understanding of the evolutionary relationship between lymph node and distant metastases is critical.

Methods: We conducted a systematic review of 1373 patient records and initially identified 19 colorectal cancer patients for whom formalin-fixed and paraffin-embedded samples from primary tumors (P), lymph node (L) and distant metastases (M) were available. We collected multiple tumor regions for each patient for a total of 239 samples. Of the 19 patients, 17 had liver metastases, one had an ovary metastasis, and one had multiple metastases in the omentum. To trace the evolution of these cancers, we used a methodology that leverages insertion/deletion mutations in hypermutable, non-coding polyguanine repeats. The mutation rate of polyguanine repeats is several orders of magnitude higher than the mutation rate of non-repeti-

tive DNA, making these sequences a rich reservoir of neutral somatic variation. We collected polyguanine genotypes across all samples and implemented rigorous purity criteria, eliminating 11% of specimens from our study (which led to the exclusion of two patients from further analyses). For all specimens belonging to the same patient, we then calculated a pairwise distance measure over all polyguanine repeats. This distance reflected how much the samples had genetically diverged and formed the basis of phylogenetic reconstruction with the neighbor-joining algorithm.

Results: We examined all phylogenetic trees according to formal criteria. We reasoned that lymph node and distant metastases had a common origin if a patient's tree contained a clade that contained at least one lymph node and at least one distant metastasis, but no primary tumor samples. Existence of such a branch indicates that both types of metastases were seeded from the same subclone, or that lymph node metastases gave rise to distant metastases. A patient was classified as having distinct origins of lymphatic and distant metastases if no such clade existed. In 6 out of 17 tumors (35%), we found a common origin of lymphatic and distant metastases. For example, Patient C38's cancer (Fig. 1) spread to the omentum and to the mesenteric lymph nodes. Furthermore, several satellite nodules had formed within the colonic epithelium, spatially separated from the primary tumor. We also investigated a piece of tumor that had invaded a vein. Notably, phylogenetic reconstruction showed that all lesions whose formation had depended on cell migration shared common ancestry, while the primary tumor had a divergent genetic profile. Cancers in the distinct origins group, which encompassed 11 out of 17 patients (65%), contained multiple, genetically distinct metastasis ancestors. Patient C66's tumor (Fig. 1) is a representative example of the distinct origins category. The cancer harbored multiple subclones at different stages of evolution that had seeded genetically distinct metastases. The tree shows that lymph node metastases were seeded continuously throughout the development of the tumor, but did not metastasize further. The liver metastases, on the other hand, arose in later evolution stages from the genetically most advanced clone. We did not observe any significant differences in the number of positive nodes, the lymph node ratio, the number of sampled primary tumor regions, the distribution of primary tumor sizes, or the fraction of patients with synchronous vs. metachronous distant metastasis between origin categories. Most importantly, we found no association between origin and treatment history, indicating that our origin classification was not influenced by any clinicopathologic variables.

Conclusion: In most colorectal cancer patients, lymph node and distant lesions have distinct subclonal origins in the primary tumor (Fig. 2). If independent seeding is prevalent, why are lymphatic and distant metastases correlated? We hypothesize that most cells in distinct origins tumors have the ability to metastasize. Establishing lymph node metastases may be a more efficient process than establishing distant metastases and may therefore happen earlier and more frequently. We conclude that lymph node metastases do not have a causal role in the development of organ metastases in most cases.

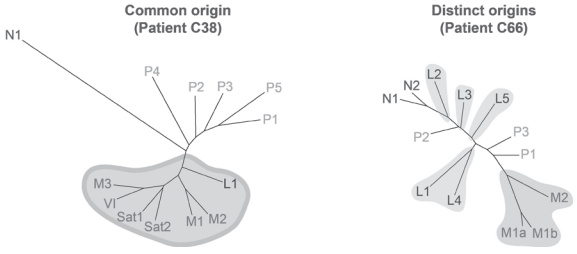

Fig. 1

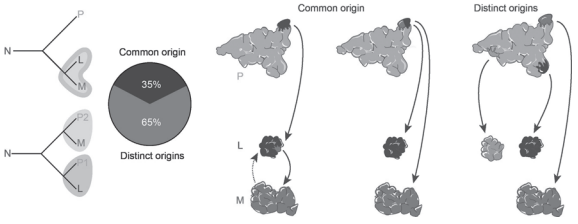

Fig. 2

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Flavia C. Nery, PhD, Center for Human Genetic Research (CHGR)

Using Connectivity Map (CMap)/L1000 to generate a transcriptome database from whole blood and tissue derived RNA from SMA patients and controls

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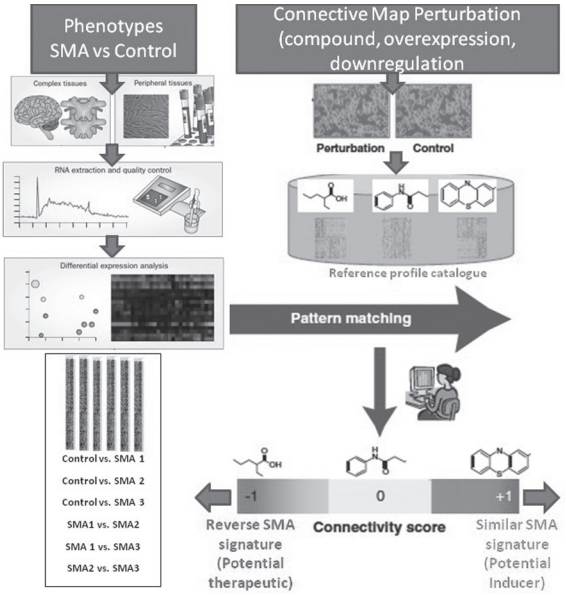
Introduction: To date, no large scale transcriptomic data exist for human derived SMA samples. The Connectivity Map (CMap) is a database of transcriptional signatures from cell lines treated with chemical and genetic reagents. When paired with the high-throughput L1000 gene expression assay by using a pattern-matching algorithm, the CMap links compounds with disease phenotypes. These tools have been applied successfully in dozens of published cases, and has led to the identification of agents with *in vivo* proof-of-concept against biologies as diverse as skeletal muscle atrophy (Kunkel et al., Cell Metabolism 2011), hair loss (Ishimatsu-Tsuji et al., FASEB J 2009), inflammatory bowel disease (Dudley et al., Science

Translational Medicine 2011), glucocorticoid resistance (Wei et al., Cancer Cell 2006), osteogenesis (Brum et al., PNAS 2015), and obesity (Liu et al., Cell 2011). In collaboration with the Broad Institute of MIT & Harvard we are applying the L1000 assay and CMAP to a diverse set of whole blood and tissue derived RNA samples from SMA patients to identify differences in transcriptional signatures that may vary by SMA type, disease severity, and other secondary disease manifestations.
Methods: In this study, over 1000 RNA samples from SMA type 1, 2 and 3 subjects and 150 RNA control samples were profiled using the L1000 gene expression assay. The implementation of transcriptome analysis in combination with the validation procedure using control samples from blood, CNS (spinal cord/brain), and systemic organs is the first step towards determining whether such an approach may be useful to identify important underlying biologic mechanisms related to disease pathogenesis and potential new treatment targets. In our initial analysis, we used R package Limma and perfomed few comparisons, such as: a) analysis of SMA samples vs. controls comparing by age groups (0-3 months; 3-6 months; >3-6 months; >6-12 months; >1-3 years; 3-6 years; >6-12 years; >12-20 years; and >20 years), and b) analysis of samples fro subjects with SMA treted or not with valproic acid (VPA) to identify genes that change robustly after treatment.
Results: Our data involved transcriptome analysis from 212 type 1, 328 type 2, 521 type 3 (a/b), 64 disease control, and 90 healthy control RNA samples. We investigated whether transcriptional changes seen in whole blood parallel those from previous studies in animal models. We confirmed significant dysregulation of pathways such as apoptosis and DNA replication, DNA replication and cell cycle regulation. We also showed that immune gene pathways and inflammatory response were notably down-regulated in SMA compared to controls. Finally, our data also supported that valproic acic (VPA) treatment reverses the "SMA type 1 signature" in infants in the SMA type 1 study pre and post treatment. In addition, we are profiling RNA from both systemic and central nervous system (CNS) tissues obtained from 14 SMA type 1 autopsy cases and age-sex matched controls to further develop a database to reflect gene expression signatures from CNS and peripheral tissues for SMA.
Conclusion: In this study present a transcriptomic analysis of whole blood from SMA infants, children and adults using L1000 microarray approach. We studied differential expression of individual gene transcripts and gene sets in four independent SMA cohorts (SMA type 1, 2, 3a, and 3b) vs. controls. We investigated whether transcriptional changes seen in whole blood parallel those from previous studies in animal models. We confirmed significant dysregulation of many pathways including DNA replication and cell cycle regulation. We also showed that immune gene pathways and inflammatory response were notably down-regulated in SMA compared to controls. This data demonstrates that whole blood transcriptome analysis may be a useful peripheral biomarker for ascertaining response to treatment for a given therapy. Further studies are needed to validate our findings in cells and tissues from subjects with SMA.



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Chee Yuan Ng, M.D., Medicine - Cardiology

Direct Ultrasound Visualization in Combination with Micropuncture Needle Reduces Vascular Access Complications in Cardiac Electrophysiological Procedures.

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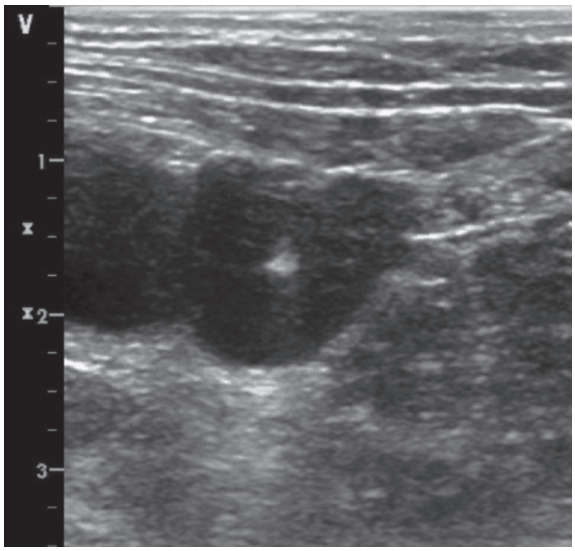
Introduction: Vascular access complications are among the most common complication encountered after electrophysiological procedures. Previous studies evaluated real-time ultrasound (US) guidance and micropuncture needle for vascular access separately but not in combination.

Methods: 182 consecutive patients undergoing cardiac electrophysiological procedures were included in the study. Vascular access was performed under direct US visualization of the 21 G needle. When prescribed, anticoagulation was continued during the procedure. The control group consists of 162 consecutive patients who underwent vascular access with a standard 18 G needle. Major vascular complications were defined as hematoma requiring intervention, arterial pseudoaneurysm and arterio-venous fistula.

Results: The most common procedure performed was ablation for atrial fibrillation which accounts for 54% of all procedures. 12% of procedures were ablation for ventricular tachycardia, and other procedures accounted for the remaining 34% of the procedures. 0/182 (0%) major vascular complications were identified in the study group compared to 6/162 (3.7%) in the control group (p=0.01).

Conclusion: Direct US visualization in combination with micropuncture needle significantly reduces major vascular complications compared to a standard 18 G needle without ultrasound guidance.

Complication	Control (n-162)	Study (n-182)	P Value
Arterial Pseudoaneurysm	4 (2.5%)	0 (0%)	0.048
Hematoma requiring intervention	2 (1.2%)	0 (0%)	0.22
Arterio-venous fistula	0 (0%)	0 (0%)	N/A
Total	6 (3.7%)	0 (0%)	0.01



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Showly Nicholson, B.A., Medicine - Hematology/Oncology

Perceptions of Prognosis and Treatment Risk in Older Patients with Acute Myeloid Leukemia (AML)

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Introduction: Older patients (≥ 60 years) with AML face difficult treatment decisions. They can choose risky, multi-drug 'intensive' chemotherapy requiring a 4-6 week hospitalization for a small chance of a cure, or 'non-intensive' and non-curative palliative chemotherapy. To make informed decisions about their treatment, patients must have a strong prognostic understanding and know the overall risks of these treatments. However, no published studies have described perceptions of prognosis and treatment risk in patients with AML.

Methods: We conducted a longitudinal study of older patients newly diagnosed with AML at two tertiary care hospitals. At enrollment, we assessed patients' and oncologists' perception of the treatment decision-making process and treatment-related mortality. At one month, we assessed patients' and oncologists' perception of prognosis using the Prognosis and Treatment Perception Questionnaire. We also examined whether patients discussed their end-of-life care wishes with their oncologist at 24-weeks. We generated descriptive statistics for all variables and stratified one-month patient data by chemotherapy type (intensive versus non-intensive).
Results: We enrolled consecutive patients within 72 hours of initiating intensive (n = 50) or non-intensive (n = 50) chemotherapy. The majority of patients (66.0%, 66/100) and their oncologists (84.3%, 75/89) perceived treatment decisions to be driven by the patient. The majority of patients reported they were at least 'somewhat' likely to die due to treatment (91.3%, 84/92) while their oncologists reported that it is 'very unlikely' (80.4%, 74/92) for the patient to die due to their treatment (P < 0.001). Although most patients (95.1%, 77/81) reported it was 'very important' to know their prognosis, the prognostic understanding of patients receiving both the intensive and non-intensive chemotherapy was significantly different from their oncologists' (Table 1). Among patients receiving intensive chemotherapy, 97.6% reported that they are 'somewhat' or 'very likely' to be cured, while 58.0% of their oncologists reported that cure was unlikely (P < 0.001). Among patients receiving non-intensive chemotherapy, 82.1% reported that they are 'somewhat' or 'very likely' to be cured, while 90.0% of their oncologists reported that cure was unlikely (P < 0.001). By 24 weeks, most patients (77.8%, 42/54) had not discussed their end-of-life care wishes with their oncologists.
Conclusion: Newly diagnosed, older patients with AML recognize the importance of knowing their prognosis and they perceive their treatment decisions to be driven by them. However, they have substantial misperceptions regarding the risks of their treatment and they overestimate the likelihood of cure compared to their oncologists' estimates. Prognostic misperceptions are especially striking in patients receiving non-intensive chemotherapy. Despite the oncologists' assessment that their prognosis was poor, the majority of older patients with AML did not report having a discussion about their end of life care preferences with their oncologists 24 weeks after initiating therapy for their disease. These data underscore the critical gaps in communication and prognostic understanding for older patients with AML. Interventions are needed to improve communication with oncologists and to ensure older patients with AML have an accurate understanding of their treatment risk and prognosis to make informed decisions about their treatment.

Table 1

Perception of Cure	Intensive Chemotherapy N = 50			Non-intensive Chemotherapy N = 50		
	Patient	Oncologist	P-value	Patient	Oncologist	P-value
Unlikely	2.4%	58.0%		17.9%	90.0%	
Somewhat Likely	36.6%	42.0%	< 0.001	38.5%	10.0%	< 0.001
Very Likely	61.0%	0.0%		43.6%	0.0%	

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Chloe K. Nobuhara, BS, Neurology

MassGeneral Institute for Neurodegenerative Disease (MIND) Cerebrospinal Fluid Tissue Bank for Biomarker Discovery

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Introduction: The purpose of the MassGeneral Institute for Neurodegenerative Disease (MIND) Tissue Bank is to collect and distribute cerebrospinal fluid (CSF) and associated clinical information to qualified researchers. CSF reflects the biochemical milieu of the brain. Diverse assays of the nucleic acid, protein, carbohydrate, lipid and metabolic composition of CSF are rapidly improving in their utility. Developing reliable biomarkers will inform diagnosis, mechanistic understanding, and tracking of disease progression. The MIND Tissue Bank contains CSF from subjects diagnosed with a range of neurodegenerative and other central nervous system diseases.
Methods: Samples are collected from consenting participants in conjunction with clinically-indicated lumbar punctures through the Outpatient and Inpatient Neurology services at Massachusetts General Hospital (MGH). Subjects are asked to donate 10-15cc of spinal fluid for research. After sufficient sample has been collected for clinical lab purposes, additional CSF is collected into low-adherence polypropylene tubes. CSF is then aliquotted into 500µl fractions and stored in siliconized-polypropylene cryotubes at -80°C within 5 hours. The participant's medical record number is assigned a de-identified alphanumeric code which exists on a limited-access, secure database. Clinical data is obtained through a systematic review of subjects' electronic medical record. De-identified samples are stored at MGH for distribution to qualified researchers.
Results: The MIND Tissue Bank has collected CSF and curated clinical data from 306 subjects to date. Ages range from 18 to 100 years of age (mean = 57.8 years, standard deviation = 18.2 years), including 152 (49.4%) males and 156 (50.6%)

females. Diagnoses are ascertained based upon review of all available records. The most common diagnoses in this cohort are Alzheimer's disease (AD) = 40, Idiopathic Intracranial Hypertension (IIH) = 34, Normal Pressure Hydrocephalus (NPH) = 30, Peripheral neuropathy = 13, Autoimmune etiology = 12, Infectious etiology = 11, Behavioral variant Frontotemporal Dementia (bvFTD) = 8, Cranial neuropathy = 7, Vascular dementia = 5, Parkinson's disease = 5, Multiple Sclerosis (MS) = 4, Primary Progressive Aphasia (PPA) = 3, Motor neuron disease = 2, Paraneoplastic syndrome = 1, Posterior Cortical Atrophy (PCA) = 1, Lewy Body Dementia (LBD) = 1, Multiple System Atrophy (MSA) = 1, Progressive Supranuclear Palsy (PSP) = 1, Traumatic Brain Injury (TBI) = 1, Corticobasal degeneration = 1, and Creutzfeldt-Jakob disease = 1. Eight ongoing and completed research studies have requested CSF from the MIND Tissue Bank to investigate diseases of the nervous system. For many cases with neurodegenerative diseases, longitudinal data is available via standardized follow-up assessments in the MGH Memory Disorders Unit.

Conclusion: Due to the broad scope of inclusionary criteria and a wide range of diagnoses, researchers can request de-identified samples from subjects with diverse diseases of interest. We look forward to continuing the expansion of this database and collaborating with researchers pursuing biomarker discovery projects.

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Ariana Y. Nodoushani, Psychiatry

Resiliency Scale Pilot Study: A Comparison of Resiliency Among Pediatric Endocrine, Psychiatry, and Burn Patients

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Introduction: Resiliency is characterized as positive growth in the face of adversity. Resilience has been associated with various promotive factors that include individual competence (self-efficacy, self-esteem, emotion regulation), socio-emotional development, the use of environmental resources to solve problems, and a relationship with a protective and dependable guardian or caregiver. Several scales have been developed to assess resiliency; however, these scales often have greater than 25 questions and are not publicly available for use. Therefore, given the need for a more concise scale, a six item Resiliency Scale (RS) was constructed based on previous literature. Using this newly created scale, this study aims to pilot the RS as a means to compare resiliency among an array of children with traumatic hardship that require significant psychological and physical rehabilitation, specifically among children with pediatric diabetes or endocrine disorders, children with psychiatric concerns, and children who have sustained burns.

Methods: The Resilience Scale (RS) and 17-Item Pediatric Symptom Checklist (PSC-17) were simultaneously distributed to the parents or guardians of children waiting to be seen in the MGH Pediatric Endocrinology Program and Diabetes Center as part of a pilot study to explore psychosocial issues in these patients. These two scales were also administered to parents or guardians of patients under 18 years of age at the Child and Adolescent Psychiatry Service at MGH as a part of routine outpatient clinic visits. Lastly, patients at Shriners Hospitals for Children – Boston aged 5 through 18 years with a burn injury covering either ≥5% of their total body surface area (TBSA) or to a critical area (i.e. face, hands, feet, genitalia) were eligible to complete the RS and PSC-17. The RS questionnaire consisted of six questions scored on a three point Likert-scale (0= "Not True" 1= "Somewhat True" 2= "Very True"). Children were reported to have low resiliency if the sum of their scores was ≤8 and high resiliency if the sum of their scores was >8. The PSC-17 is a psychosocial screening questionnaire consisting of 17 items that are rated as "Never", "Sometimes", or "Often", corresponding to scores of 0, 1, and 2, respectively. Children whose total score sums to ≥15 are considered to be "at risk" for psychosocial problems. Descriptive statistics were run using SPSS v-24. The administration of these questionnaires in the Pediatric Endocrinology Program and Diabetes Center, Child and Adolescent Psychiatry, and Shriners Hospital for Children – Boston were part of individual IRB approved studies.

Results: Surveys were collected from the parents of 274 children – 88 pediatric diabetes or endocrine disorder subjects, 172 child psychiatry subjects, and 14 burn subjects. The mean age of children was 12.10 ± 3.77 and did not significantly differ amongst diagnoses. Of the total sample, 92 (33.58%) children scored low resiliency: 9 (10.23%) of 88 diabetes or endocrine subjects, 2 (14.29%) of 14 burn subjects, and 81 (47.09%) of 172 child psychiatry subjects. Seventy-three (26.64%) children of the total sample population were reported to be "at risk" on the PSC-17: 5 (5.68%) of 88 diabetes or endocrine subjects, 3 (30%) of 10 burn subjects, and 65 (37.79%) of 172 child psychiatry subjects. The rates of low resiliency and "at risk" classifications on the RS and PSC-17, respectively, differed significantly between each population ($p<0.001$). Four (44.44%) of 9 children with diabetes or endocrine disorders, 50 (61.73%) of 81 children with psychiatric concerns, and 1 (50%) of 2 children with burns also scored "at risk" on the PSC-17. Out of all the low resiliency children, 55 (59.78%) of 92 were reported to be

"at risk" under the PSC-17 ($p<0.001$). The rates of low resiliency children "at risk" under the PSC-17 differed significantly within each population as well as within the total sample population ($p<0.001$).
Conclusion: This study suggests that among children with an array of pediatric traumatic hardship, children with psychiatry concerns exhibit the highest prevalence of low resiliency followed by children who have sustained burns and those with pediatric diabetes or endocrine disorders. Children with psychiatric concerns additionally have the highest prevalence of "at risk" children under the PSC-17 followed by children with burns and those with pediatric diabetes or endocrine disorders. Furthermore, the low resiliency child psychiatry patients had the greatest prevalence of risk on the PSC-17 compared to the pediatric diabetes or endocrine disorder patients and burn patients. These findings suggest that children with psychiatric concerns may be more likely to have low resiliency compared to children with diabetes or endocrine disorders and children with burns. Since more than half of children with low resiliency are reported to be at risk under the PSC-17, it is necessary to further examine a child's cognitive, behavioral, and emotional problems to understand resiliency. While there are limitations to this study with regards to the small sample size and non-uniform inclusion criteria, this preliminary data informs next steps for a prospective study to validate the RS with other standard resiliency scales. A normative sample from a population of healthy children should be collected for a more extensive exploration into resiliency in pediatric populations that experience trauma such as burns, pediatric diabetes or endocrine disorders, or mental health conditions.

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Sarah O'Dor, Psychiatry

Effects of ADHD Symptoms on Medical Adherence: Are EF deficits extra hurdle for T1Diabetes?

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Introduction: Poor adherence to clinical guidelines is a pervasive and dangerous problem for children and adolescents with Type 1 Diabetes (T1D).[1] Children with executive functioning (EF) deficits, including those with Attention Deficit Hyperactivity Disorder (ADHD), exhibit symptoms that may impact adherence. The relationship between EF deficits, adherence, and glycemic control has been mixed.[2] This study aims to address: 1. Do ADHD symptoms impact adherence of pediatric T1D patients? 2. Do different types of insulin delivery (i.e., continuous subcutaneous insulin infusion (CSII) or multiple daily injections (MDI)) lead to different outcomes? 3. Is there a relationship between demographic variables and clinical adherence and glycemic control? 1. Amed, S. et al. (2013). Adherence to clinical practice guidelines in the management of children, youth, and young Adults with type 1 diabetes—A prospective population cohort study. The Journal of Pediatrics, 163(2), 543-548. 2. Duke, D.C. & Harris, M.A. (2014). Executive function, adherence, and glycemic control in adolescents with type 1 diabetes: A literature review. Current Diabetes Reports, 14, 153.
Methods: Participants: Patients ages 12-17 years with Type 1 diabetes recruited from the MGH Pediatric Endocrinology Clinic. Our study sample consisted of 26 children with mean age of 14.77 years (SD = 1.75 years). Eighty percent of the study sample was white and 46.2 percent were female. Measures: 1. Demographic questionnaire 2. Diabetes Behavior Rating Scale (Parent and Self-Report) 3. Conners (Parent and Self-Report) 4. Hemoglobin A1C (HbA1c) 5. Episodes of Ketoacidosis (DKA) 6. Episodes of Hypoglycemia Analyses: Aim 1: One-tailed Pearson's bivariate correlations between four variables: parent report of child's adherence to diabetes regimen, child report of adherence, parent report of child's ADHD symptoms, and child report of ADHD symptoms. A Bonferroni Correction (.05 x 4 = 0.0125) was applied. Aim 2: Independent t-tests were conducted to determine if type of insulin delivery was related to HbA1C. Aim 3: Pearson's bivariate correlations and Spearman's rank order were used to determine if demographic variables predict HbA1C and child and parent report of adherence.
Results: Illness Variables: In the study sample, duration of illness ranged from 1 to 16 years (M = 7.54 yrs; SD = 4.29). Average HbA1C at the time of the study ranged from 7.5 to 12.2 (M = 9.0; SD = 1.2). The majority of participants were on CSII (73.1%). Only one participant (3.8% of total) had DKA in the past year. Approximately 27% of participants experienced at least one episode of hypoglycemia in the past year. Results: Aim 1: Results showed a significant relationship between low levels of adherence (parent report) and high level of ADHD symptoms (child report), $r = -.526$, $n = 18$, $p = .012$. Aim 2: No significant differences were found in HbA1C between groups (i.e., CSII vs MDI). Aim 3: In our sample, no significant relationships existed between gender or length of illness and HbA1C or parent or child report of adherence.
Conclusion: Research Implications: In this study sample, insulin delivery method (CSII or MDI) was not related to diabetes management outcomes (HbA1C). This may be due to the low number of patients on MDI and should be repeated with a larger sample; or may reflect the challenges of diabetes management in adolescence regardless of management method. Clinical Implications: Children who experience more ADHD symptoms (per child report) were less adherent to their diabetes regimen (per parent report). This suggests the importance of screening using both parent and adolescent report to assess for psychological factors impacting diabetes adherence.

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Sharon Odametey, Dermatology

Retrospective Evaluation of Two Telemonitoring Interventions for Heart Failure Patients

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Introduction: Heart failure (HF) is a significant health problem in the United States (US) which worsens over time and is associated with repeated hospital admissions. A comprehensive post-discharge treatment plan involving patients, caregivers, and care providers is needed to achieve optimal clinical outcomes. Telemonitoring (TM) is a commonly used solution to help healthcare providers monitor patients remotely and intervene before clinical deterioration of the patient occurs. Studies suggest that TM solutions may reduce heart failure hospitalizations and mortality in certain populations. Partners Healthcare at Home, a homecare providing entity of the Partners HealthCare System, refers patients to 2 different TM solutions: 1) Philips telemonitoring (PTM), an intensive solely home-based solution which has been used at PHH for the past 10 years, and 2) iGetBetter (iGB), a completely mobile, albeit less intensive, solution which was developed in 2013. Both augment care and disease self-management in patients with heart failure by allowing patients to monitor their vitals and share readings with their care team from the comfort of home. While iGB leverages commonly used mobile and portable consumer devices (weight scales and tablets), the PTM solution is not mobile. The goal of this study was to compare outcomes of iGB and PTM in a non-inferiority analysis. Study outcomes were assessed by the rate of inpatient admissions and cost of inpatient healthcare utilization both before and after TM intervention.
Methods: This study evaluated medically stable, ambulatory congestive heart failure patients aged 18 years or above who received care through either the iGB or PTM platform between Dec. 2015 – Dec. 2016 for at least a week, and no longer than 3 months. Patient data was extracted for the duration of each patient's intervention enrollment, 2 months prior to their start date, and 2 months after their end date. To analyze rate of inpatient admissions, we used Chi-square tests for between group comparisons of patients with admissions before and after TM intervention, and McNemar's test for within group comparisons of patients who had admissions before and after TM intervention. To analyze cost of healthcare utilization, we used linear models controlling for potentially confounding factors to compare between groups at each time point.
Results: 28 iGB and 83 PTM patients were included in the analyses. The iGB group was overall younger than the PTM group (median 74 v. 82, $p = 0.02$). The groups were otherwise demographically similar, thus age was included in the linear model for comparing healthcare cost. Median intervention period for both groups was 2 months. The percentage of patients who had admissions before and after enrollment was similar between groups (chi-square before $p = 0.33$, after $p = 1.00$). Both groups saw a decrease in the number of patients with inpatient admissions post-intervention. McNemar's test for risk of inpatient admission before or after the enrollment period was significant for both groups at $p = <0.01$. Linear models controlling for age before ($p = 0.89$), during ($p = 0.42$), and after ($p = 0.74$) intervention reveal no between-groups difference in healthcare cost at any timepoint. Though there were fewer inpatient admissions post- compared to pre-intervention – and thus total inpatient costs decreased (-65% for iGB, -42% for PTM) – median cost and average cost per admission and per patient increased.
Conclusion: Clinical and cost outcomes did not differ by type of heart failure telemonitoring interventions. An adequately powered trial will be needed to comprehensively evaluate impact of both interventions.

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Emily A. Ohrtman, BA, Physical Medicine and Rehabilitation

The Impact of Burn Injury on Social Interactions and Social Activities: A Life Impact Burn Recovery Evaluation (LIBRE) Study

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Introduction: While recent advances in burn care have decreased the mortality after burns, research focusing on the psychosocial needs of burn survivors remains limited. Interactions with strangers and participation in social activities are key components of social recovery. However, the disfigurement that results from injury can make this difficult and provoke anxiety among survivors. Currently, very little objective information has been collected on social activities and social interactions post burn injury. The objective of this work is to better understand these areas of social recovery using the Life Impact Burn Recovery Evaluation (LIBRE) Profile, a cross-sectional survey engineered by the LIBRE Project.

Methods: The LIBRE Profile contains 192 items and examines six scales of social participation, including the Social Interactions scale (25 items) and Social Activities scale (15 items). In these scales, a higher score indicates more social participation. All participants were 18 years or older and had injuries greater than 5% total body surface area or burns to critical areas (hands, feet, face, or genitals). Of the 601 participants who were recruited, 599 completed the Social Interactions scale and the Social Activities scale. Linear regression analyses were used to determine demographic and clinical predictors of the Social Activities and Social Interactions scores. Finally, the percentages of participants who reported low scores for each item within the Social Activities and Social Interactions scales were calculated.
Results: Within the final study sample, 55% of the population were female. Most participants identified as White Non-Hispanic (77%) and had an education level of high school or less (41%). Over half of the participants were not married (55%) and over 80% of the participants had burns to critical areas. Participants had a mean age of 45 years and a mean time since burn injury of 15 years. In the Social Activities linear regression analysis, older age ($p<0.01$) and those who were not married or not living with a significant other ($p=0.01$) were associated with lower predicted scale scores. Similarly, older age and those not married or not living with a significant other were associated with lower Social Interactions scale scores ($p<0.01$). Male participants and those with higher education levels had higher Social Interactions scale scores ($p<0.01$). However, in the Social Activities linear regression analysis, only higher education levels were significantly associated with higher scale scores ($p<0.01$). In the Social Activities scale, participants reported low scores on items relating to avoidance of outdoor activities (30%), limitations on what they can do with their families (25%), and tiring easily when doing things that are fun (23%). In the Social Interactions scale, participants reported low scores on items relating to dressing to avoid stares (32%), avoidance of things that might call attention (26%) or worrying about other's attitudes (25%).
Conclusion: Interactions with the public and participation in social activities are long-term challenges for burn survivors. Older individuals and those that do not interact with a spouse or significant other at home may have a harder time with social activities and interactions. In particular, burn survivors may have trouble participating in outdoor activities or activities with their families. Burn survivors may also feel uncomfortable with their appearance and struggle with anxiety over unwanted attention and other's attitudes. This study's cross-sectional design and potential selection bias may limit the generalizability of these findings to the greater burn survivor population. Nonetheless, the severity of this study's findings show that more research and clinical support are needed in relation to burn survivor's social recovery and reintegration.

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Laura Ortiz-Terán, MD PhD, Radiology

Brain Circuit-Gene Expression Relationships and Neuroplasticity of Multisensory Cortices in Blind Children.

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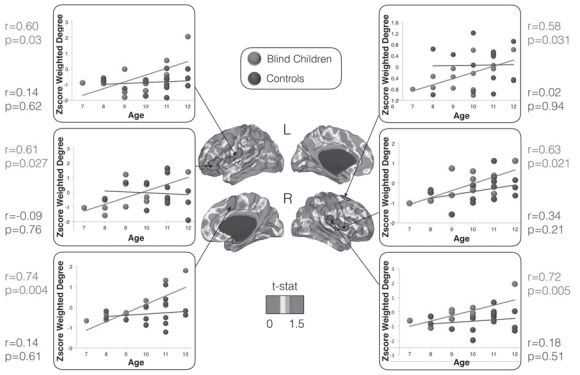
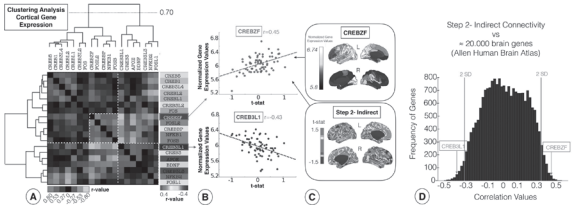
Introduction: Cross-modal neuroplasticity has been proposed as a mechanism by which individuals without sight recruit visual-related cortices to process sensory information from other perceptual modalities. We have previously observed in adults with blindness compared to healthy subjects that multimodal integration regions are prominent sites of neuroplastic reorganization. In this study we have delineated cortical connectivity profiles and examined the relationship between neuroplastic alterations and experience-dependent gene expression profiles in the cerebral cortex.
Methods: We studied 13 children with blindness (N=9 boys) ages between 7-12 years old (mean=9.6±1.3), and 15 sighted controls (N=6 boys) (mean=10.3±1.4). Subjects were scanned on a 3T MRI scanner, acquiring BOLD and high-resolution 3D T1WI. Following preprocessing, whole brain weighted-degree functional connectivity and step-wise connectivity graph theory analyses were applied.
Results: In weighted-degree analyses corrected for multiple comparisons, blind children exhibited enhanced connectivity in bilateral ventral premotor, middle cingulate cortex/supplementary motor area and right temporal parietal junction. Several of these connectivity changes positively correlated with age (Figure 1). Using step-wise connectivity analysis, blind children compared to controls demonstrated increased functional streams along certain multimodal integration regions such as the anterior insula and temporoparietal junction bilaterally and right lateral occipital cortex. When we correlated gene expression profiles with the main connectivity changes in blind subjects in the indirect connectivity, the topological distribution of sensory-system connectivity reorganization showed a robust positive correlation with the expression patterns of the certain members of the CREB family (Figure 2).
Conclusion: Blind children show increased functional connectivity in multimodal integration areas compared to controls, and older children showed greater increases within these regions and that this reorganization was highly spatially associated with a family of genes directly involved in neuroplasticity, the CREB (cAMP Response Element Binding protein) family.

Using systems-level and genetic analyses, this study advances our knowledge of human neuroplasticity following sensory deprivation. Understanding the changes in neuroplasticity developed in blind children, is critical for future clinical and neuroeducational interventions.



The Effect of Age on the Connectivity Pattern of Blind Children. Connectivity changes in multimodal integration regions were positively correlated with age in blind children. A color scale map based on t-values is shown with red areas representing the effect of age (i.e., regions with increased connectivity with age) and black lines delineating statistically significant regions corrected for multiple comparisons. Parietal operculum/ventral premotor cortex (OP4/vPM), supplementary motor area (SMA), Pars Triangularis, Parietal Operculum (OP1), medial (Med), and lateral (Lat). In the scatter plots, the connectivity at each significant region is displayed for each subject, with values for blind children shown in red and those of controls shown in blue. The correlation coefficients and p-values are presented next to each region, again in red for blind children and blue for controls.



Brain Plasticity-Gene Expression Relationships in Blindness. Functional connectivity changes in multimodal integration areas are positively associated with the degree of neuroplasticity-related gene expression. **Panel (a)** Analysis of the relationship between transcription levels of neuroplasticity-related genes and indirect connectivity changes in blind children compared to their controls. **Panel (b)** The topological cortical distribution of sensory-system connectivity reorganization showed a highly positive spatial similarity with the magnitude of CREBZF gene, while CREB3L1 showed highly negative spatial relationships. **Panel (c)** The spatial distribution of the CREBZF gene and functional connectivity changes in the indirect connectivity analysis. **Panel (d)** Histogram presenting the location of CREBZF and CREB3L1 in comparison with the rest of topological similarities between approximately 20,000 genes and the map of connectivity changes in blind subjects.

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Jamel P. Ortoleva, M.D., Anesthesia, Critical Care and Pain Medicine

Echocardiographic Evaluation of Biventricular Function during ECMO

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Introduction: Extra corporeal membrane oxygenation (ECMO) is an evolving therapy with increasing utilization across the world. According to the ELSO registry, ECMO centers in the mid 2000s numbered at approximately 130 with about 2000 reported cases to 305 centers with 7368 cases in the year 2016. Currently, the exact role of ECMO is yet to be fully delineated with respect to patient selection, timing, indications and contra-indications. There are two main ECMO modes, Veno-venous and Veno-arterial. We collected data for both cannulation strategies. In what follows, we describe our institutional experience in adult ECMO in the interval of 2009 to 2016 covering 265 patients over multiple intensive care units and varying settings. As we are a regional referral center for this patient population, we included both transfers and in house referrals.

Methods: After obtaining IRB approval, we retrospectively reviewed the charts of all 265 ECMO patients and reported echocardiographic (both transthoracic and transesophageal) findings in the peri-ECMO period. Specifically we collected left and right ventricular ejection fraction and/or systolic function at three time points: pre ECMO cannulation, during ECMO cannulation, and post ECMO decanulation when available. Cardiac function while on ECMO was determined by the study performed in the middle of the time interval of ECMO cannulation. We sought to answer the following questions in our analysis: 1) what is the mortality overtime in patients placed on ECMO 2) Do the interval assessments of LV and RV function prognosticate (with respect to mortality)?

Results: In total, 129 of 265 patients survived. Survival was defined as being alive 30 days after ECMO cannulation. On the whole, VV ECMO survival was 53.13% versus 41.36% for VA ECMO (P = 0.11). For ventricular function Grades 1 through 5 were used to represent akinetic, severely depressed (EF < 30%), moderate (EF 31-40%), mild (EF 41-50%), and normal (EF >50 %) ventricular function with 1 being worst and 5 being normal. Overall for both VA and VV ECMO, in patients that survived, LV function showed improvement comparing pre and post-ECMO (3.63 vs 4.31 [P <0.000]). Similarly RV function showed improvement comparing pre and post-ECMO (3.25 vs 4.13 [P <0.0001]). This improvement was nearly a full grade improvement, showing some clinical significance. In patients that survived on VA ECMO only, the difference in pre and post LV and RV function is even more marked: LV pre: 3.12 LV post: 3.95 and RV pre: 2.86 RV post: 3.95 (P Values < 0.0006). Patients who survived on V-A ECMO had statistically significantly higher post LV and RV function as

compared to those who died: LV: 3.83 vs 2.77 (P < 0.0001) and RV: 3.87 vs 3.15 (P = 0.008). No differences were noted in LV or RV echocardiographic findings for patients while on ECMO.
Conclusion: Our ECMO experience suggests that while mortality is high, echocardiography can be useful in prognostication. Statistically and clinically significant differences were noted in patients that survived and those that did not. These findings, if corroborated, may assist in decision making and ECMO utilization.

Patient data and demographics

Age	50.7±14.9
ECMO Duration	9.3±17.8 days
Mode of ECMO	
VA	165 (62.3%)
VV	67 (25.3%)
Mixed	33 (12.45%)
2009-2013	130 (49.1%)
2014-2016	135 (50.9%)
Survived to Discharge	129 (48.7%)
Unit	
CSICU	142 (53.6%)
CCU	4 (1.5%)
MICU	43 (16.2%)
SICU	64 (24.2%)
Cath Lab	4 (1.5%)
Multiple Units	8 (3.0%)

Survivors of VA ECMO

Pre LV Function	Post LV Function	P-value
3.12	3.95	P = 0.0006
Pre RV Function	Post RV Function	P-value
2.86	3.95	P = 0.0006

Based on the American Society of Echocardiography Chamber Quantification Recommendations

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Michael T. Osborne, MD, Medicine - Cardiology

Resting Amygdalar Activity Predicts Baseline and Future Changes in Adiposity: A Mechanism Linking Chronic Stress and Obesity with Cardiometabolic Implications

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Introduction: While chronic psychosocial stress has been linked to obesity, the mechanism mediating this association remains unclear. Whole body and brain ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) imaging provides a unique means of simultaneously evaluating neural and extra-neural tissue activity to better understand underlying physiology. We imaged metabolic activity of the amygdala (AA) with FDG PET/CT imaging, a measure of neural tissue response to stress that has been validated with standard psychiatric assessments, simultaneously with measurements of hematopoietic tissue (i.e. bone marrow) metabolic activity on FDG PET/CT imaging and adiposity on CT imaging to test our hypotheses that AA associates with increased baseline and subsequent adiposity and that the effect of increased AA on adipose tissue volumes is mediated by increased hematopoietic activity.
Methods: A total of 232 individuals (55±10 years) without active oncologic disease or clinically significant cardiovascular disease who underwent clinically indicated FDG PET/CT imaging for malignancy surveillance. AA, hematopoietic tissue activity and adipose tissue volumes were assessed in all individuals using validated methods. Visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) and total adipose tissue volumes were assessed by CT in all subjects at baseline and in a subset of the study population with serial imaging (N=83). Image analyses were performed by blinded investigators. Relationships between AA, adipose tissue volumes and AI were evaluated with Pearson correlation and mediation analysis.
Results: At baseline, AA (as a continuous variable) associated with body mass index (BMI) (standardized β [95% CI]=0.15 [0.03-0.26], p=0.014), VAT (0.19 [0.07-0.30], p=0.002), and VAT/SAT ratio (0.20 [0.07-0.30], p=0.002) in univariate models, and the association largely remained robust to multivariate adjustment, including for age, gender and baseline BMI (**Table 1).** In subjects with serial imaging over a follow up interval of 354 +/- 128 days, AA predicted subsequent progression of VAT (standardized β [95% CI]=0.43 [0.30-1.00], p<0.001) and total fat (0.32 [0.09-0.56], p=0.009) in univariate models, and the association largely remained significant in multivariate models with age, gender and baseline measurements of adiposity (**Table 2**). Furthermore, mediation analysis suggests that 48% of the relationship between AA and VAT was mediated by bone marrow metabolic activity (p=0.007).
Conclusion: In this first study to link neural center metabolic activity to adiposity, we show that stress (via AA) independently associates with baseline adiposity and longitudinal changes in adiposity. Furthermore, AA linked to VAT via a pathway through increased bone marrow activity, which suggests that inflammation has an important role in the link between

stress and VAT. These findings provide new insights into the mechanism by which stress may predispose humans to obesity and consequent cardiometabolic disease.

Predictor	Dependent Variable (endpoint)	Covariates	Standardized β (95% CI)	p-value
Amygdalar Activity	Baseline BMI	None	0.15 (0.03 - 0.26)	**0.014**
		Age	0.14 (0.03 - 0.26)	**0.018**
		Gender	0.15 (0.03 - 0.26)	**0.014**
	Baseline VAT	None	0.19 (0.07 - 0.30)	**0.002**
		Age	0.19 (0.07 - 0.30)	**0.001**
		Gender	0.19 (0.07 - 0.30)	**0.001**
		BMI	0.09 (-0.004 - 0.18)	0.060
	Baseline SAT	None	0.04 (-0.08 - 0.16)	0.54
		Age	0.04 (-0.09 - 0.16)	0.54
		Gender	0.04 (-0.08 - 0.16)	0.53
		BMI	-0.09 (-0.17 - -0.01)	**0.02**
	Baseline VAT:SAT	None	0.20 (0.07 - 0.30)	**0.002**
		Age	0.13 (0.01 - 0.23)	**0.03**
		Gender	0.20 (0.08 - 0.29	**0.001**
		BMI	0.20 (0.07 - 0.30)	**0.002**
	Baseline Total Fat	None	0.11 (-0.01 - 0.23)	0.07
		Age	0.09 (-0.04 - 0.21)	0.18
		Gender	0.12 (-0.01 - 0.23)	0.07
		BMI	-0.02 (-0.08 - 0.05)	0.65

Abbreviations: BMI: body mass index, SAT: subcutaneous adipose tissue volume, VAT: visceral adipose tissue volume

Table 1: Relationship between amygdalar activity and baseline measurements of adiposity.

Independent Variables		Dependent Variable (Endpoint)											
		Δ Weight		Δ VAT		ΔSAT		Δ VAT : SAT		Δ Total Fat		Δ Lean Body Mass	
Predictor	Covariates	Standardized β(95% CI)	p-value	Standardized β (95% CI)	p-value	Standardized β (95% CI)	p-value	Standardized β (95% CI)	p-value	Standardized β (95% CI)	p-value	Standardized β (95% CI)	p-value
Amygdalar Activity	Univariate	-0.09 (-0.22-0.04)	0.19	0.43 (0.30- 1.00)	**<0.001**	0.25 (0.004- 0.49)	**0.047**	0.097 (-0.15- 0.34)	0.43	0.32 (0.09- 0.56)	**0.009**	-0.1 (-0.53-0.22)	0.42
	Age	-0.06 (-0.18-0.09)	0.51	0.43 (0.31- 1.02)	**<0.001**	0.24 (-0.12- 0.74)	0.057	0.12 (-0.18- 0.54)	0.32	0.32 (0.12- 0.85)	**0.011**	-0.11 (-0.54- 0.22)	0.39
	Gender	-0.09 (-0.22-0.04)	0.19	0.45 (0.36- 1.04)	**<0.001**	0.25 (0.002- 0.76)	**0.049**	0.11 (-0.21- 0.54)	0.38	0.33 (0.014- 0.88)	**0.008**	-0.11 (-0.54- 0.21)	0.39
	Baseline BMI	-0.08 (-0.21-0.06)	0.28	0.43 (0.31- 1.02)	**<0.001**	0.26 (0.03- 0.77)	**0.035**	0.09 (-0.24- 0.52)	0.46	0.34 (0.16- 0.88)	**0.006**	-0.08 (-0.48- 0.23)	0.49
	Baseline VAT	-0.07 (-0.19-0.08)	0.41	0.42 (0.29- 1.00)	**0.001**	0.29 (0.02- 0.74)	0.06	0.10 (-0.22 0.54)	0.46	0.31 (0.11- 0.85)	**0.012**	-0.12 (-0.56- 0.17)	0.29
	Baseline SAT	-0.09 (-0.21-0.06)	0.25	0.44 (0.3- 1.01)	**<0.001**	0.26 (0.04- 0.75)	**0.032**	0.10 (-0.23- 0.53)	0.79	0.33 (0.17- 0.86)	**0.004**	-0.11 (-0.55-0.21)	0.38
	Baseline VAT:SAT	-0.08 (-0.21-0.07)	0.33	0.43 (0.31- 1.026)	**0.001**	0.25 (0.006- 0.77)	**0.047**	0.09 (-0.22- 0.49)	0.44	0.33 (0.13- 0.88)	**0.008**	-0.12 (-0.67- 0.20)	0.33
	Baseline Total Fat	-0.08 (-0.21-0.06)	0.29	0.42 (0.31- 1.00)	**<0.001**	0.24 (0.006- 0.74)	**0.046**	0.1 (-0.23- 0.53)	0.81	0.32 (0.13- 0.84)	**0.008**	-0.11 (-0.64-0.20)	0.36

Abbreviations: BMI: body mass index, SAT: subcutaneous adipose tissue volume, VAT: visceral adipose tissue volume

Table 2: Relationship between amygdalar activity and future changes in adiposity.

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Benjamin Osher, Medicine - General Internal Medicine

The cost-effectiveness of HIV pre-exposure prophylaxis in high-risk men who have sex with men and transgender women in Brazil

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Introduction: Men who have sex with men (MSM) and transgender women (TGW) in Brazil experience high rates of HIV infection. We examined the clinical and economic outcomes of implementing a pre-exposure prophylaxis (PrEP) program in these populations.

Methods: We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)-International model of HIV prevention and treatment to evaluate two strategies: the current standard of care (SOC) in Brazil, including universal ART access (*no PrEP* strategy); and the current SOC plus daily tenofovir/emtracitabine PrEP (*PrEP* strategy). Mean age (31y), age-stratified annual HIV incidence (age≤40y: 4.3/100PY, age>40y: 1.0/100PY), PrEP efficacy (86% HIV incidence reduction), and PrEP drug costs ($12.50/month) were from Brazil-based sources. The analysis focused on direct medical costs of HIV care. We measured the comparative value of PrEP in 2015 United States dollars (USD) per year of life saved (YLS). Willingness-to-pay threshold was based on Brazil's annual per capita gross domestic product (GDP; 2015: $8,540 USD).

Results: Lifetime HIV infection risk among high-risk MSM/TGW was 50.6% with *no PrEP* and decreased to 10.0% with *PrEP*. *PrEP* increased per person undiscounted (discounted) life expectancy from 36.8 (20.7) years to 42.7 (23.0) years and lifetime discounted HIV-related medical costs from $4,090 to $5,130, which led to an incremental cost-effectiveness ratio (ICER) of $460/YLS. *PrEP* remained cost-effective (<1x GDP) under plausible variation of key parameters, including PrEP efficacy and cost, initial cohort age, and HIV testing frequency on/off PrEP.

Conclusion: Daily tenofovir/emtracitabine PrEP among high-risk MSM/TGW in Brazil would increase life expectancy and be highly cost-effective.

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Gladys N. Pachas, MD, Psychiatry

Self-Reported Smoking Behavior and Cessation Experience Among Hispanic and Non-Hispanic Smokers with Serious Mental Illness

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Introduction: Addiction to nicotine is highly prevalent among those with serious mental illness (SMI). Recent estimates indicate that 64%-79% of those with schizophrenia spectrum disorders smoke tobacco regularly, as do 44-71% of those with bipolar disorder, and 43% of those with major depressive disorder. People with serious mental illness (SMI) die on average 25 years earlier than the general U.S. population. Much of this difference is attributed to cardiovascular and pulmonary diseases associated with major risk factors such as cigarette smoking. Similar rates occur among racial and ethnic minority groups. While there is little data on the morbidity and mortality associated with cigarette smoking among Hispanic people with SMI, we assume these rates are at least equivalent among this population.

Methods: Our goal was to investigate differences in self-reported smoking behavior and interactions with primary care physicians (PCP) around smoking cessation treatment between Hispanic (H) and non-Hispanic (NH) smokers with SMI. We analyzed data from a 5-minute survey among smokers with SMI in the Boston area. This study is currently enrolling smokers with SMI who receive psychiatric rehabilitation services from one of two agency partners, Bay Cove Human Services or Vinfen Corporation. Participants complete the 5-minute baseline survey (Year 1) about their smoking habits and the care they had received from their primary care doctor in the last year, followed by a carbon monoxide (CO) breath test. Participants will be asked to complete this survey on two more occasions, on an annual basis, after the intervention has been implemented (Years 2 and 3). Following the completion of baseline data collection in August 2017, primary care clinics that provide care to these smokers will be randomly assigned to receive AD to their PCPs about smoking cessation for people with SMI or treatment as usual. Participants who receive primary care through clinics assigned to the AD intervention will be randomized to be offered support from a CHW (AD+CHW) or not (AD).

Results: Of the 971 participants surveyed thus far, 16.5% self-identified as Hispanic. Average age of all participants was 47.9 years (±12.9) with Hispanic participants being significantly younger than non-Hispanic participants (H=42.3±12.4, NH=49.0±12.8, p>0.001). Preliminary baseline results indicate that 70.3% of the enrolled participants are male; this was similar among Hispanic and non-Hispanics (p=0.931). The majority of all participants smoke 11-20 tobacco products per day (32.7%), with an average expired CO reading of 22.5 ± 20.6 (n=889) and reported smoking within 5 minutes of waking (39.9%). On average, all smokers in this sample scored a 2.89 ±1.67 (n=966) on the Heaviness of Smoking Index (HSI), a measure indicating low to moderate dependence. There were no significant differences between Hispanic and non-Hispanic smokers with regard to number of tobacco products smoked per day, expired CO, or smoking within 5 mins of waking. However, Hispanic smokers had significantly lower HSI scores compared to non-Hispanic smokers (H=2.69 ±1.79, NH=2.92 ± 1.65, p=0.033). On average, 92.7% of all participants reported that their PCP is aware that they smoke. Among those who saw their PCP in the past year, 71.4% of all participants reported being advised to quit smoking. There were no significant differences between Hispanic and non-Hispanic participants. Hispanic participants report being prescribed any cessation treatment at higher, but not significant, rates than non-Hispanic participants (H=59.1%, NH=49.9%, p=0.093). Significant differences by ethnicity exist with regard to PCPs prescribing or recommending nicotine replacement therapies, specifically nicotine patches (H=32.5%, NH=23.4%, p=0.021), nicotine lozenges/gum (H=23.8.6%, NH=16.3%, p=0.030. There were no differences by ethnicity for varenicline, bupropion, cessation groups or the quit line.

Conclusion: While Hispanic smokers with SMI in our study had significantly lower HSI scores than non-Hispanics, they still register as having low to moderate nicotine dependence. More Hispanic smokers with SMI report being prescribed nicotine replacement cessation treatments by their PCP than non-Hispanics, specifically, nicotine patches, lozenges or gum. In general, rates of provision of guideline-concordant smoking cessation treatment in primary care to those with SMI are low, which likely contributes to the low rates of cessation and the subsequent mortality disparity in this population. Additional smoking cessation education for PCPs focused on smokers with SMI would likely result in more Hispanic smokers receiving more efficacious treatment options.

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Ramya Palacholla, MD, MPH, Medicine

Design of a Trial Assessing the Impact of a Risk Assessment System (CareSage) and Tailored Interventions on Healthcare Utilization

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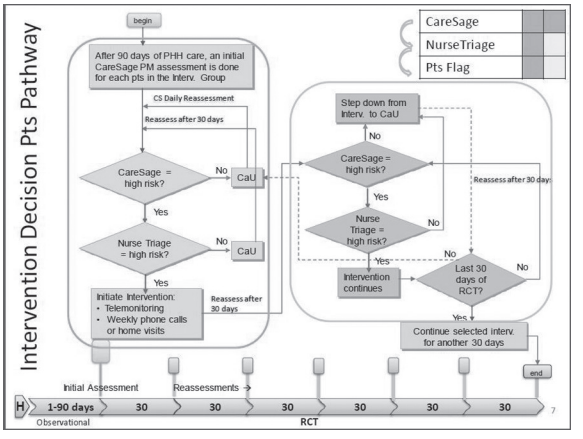
Introduction: Soaring healthcare costs and a rapidly aging population, with multiple co-morbidities, necessitates the development of innovative strategies to improve the delivery of high quality, value-based care. Multi-disciplinary interventions targeting high risk patients, who contribute heavily to the healthcare costs, have potential to improve quality of care, patient outcomes and reduce costs in the long run. The goal of this study is to evaluate the impact of a risk assessment platform (CareSage) and targeted interventions on healthcare utilization.

Methods: CareSage is a backend analytics service that utilizes both real-time and historical patient data collected from the healthcare system and a Personal Emergency Response Service (PERS). PERS consists of a button worn as a pendant that can be pushed by the patient in medical emergencies. CareSage uses a complex algorithm to predict the risk of emergency transport in patients and classifies patients in the intervention group as 'high' or 'low' risk every 30 days. All patients flagged as "high risk" by CareSage will receive nurse triage calls to assess their needs and provide tailored interventions including patient education around disease self-management and treatment adherence via telephone calls (just-in-time or staggered); home visits for an in-person clinical assessment; and telemonitoring for CHF patients. **Study Design** This is a 2-arm randomized controlled trial recruiting participants from a pool of patients receiving care at Partners Healthcare at Home. 370 patients will be randomized into either a control or intervention arm of the study. The study involves two study periods: a 3-month observation period and a 6-month intervention period. Outcomes will be evaluated at the end of the 9-month period.

Results: The study is in progress and we have enrolled 31 patients so far; results are expected by the end of 2018. **Outcomes** Primary outcomes are 90- and 180-day emergency department visits. Secondary outcomes include total medical expenses, mortality rates, time to readmission, total number of admissions and avoidable readmissions, health-related quality of life, emergency transport use, 30-day readmission rate, and total hospitalization rates. The Partners Healthcare Enterprise Data Warehouse (EDW), the Electronic Medical Records (EMR), and Phillips Lifeline databases will be used to extract data and evaluate outcomes at the end of the study.

Conclusion: Innovative clinical tools for identifying high-risk patients and targeting interventions may help facilitate the delivery of value-based care and improve long term patient health outcomes and decrease healthcare costs.

CareSage Study Design



CareSage Intervention Decision Pathway

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Jonathan Paolino, MD, Pediatrics

The Effects of a New Clinical Pathway to Guide Administration of High Flow Nasal Cannula Outside of the Pediatric ICU for Bronchiolitis Patients at MGHfC

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Introduction: Bronchiolitis is a common pediatric problem and frequently results in admission for respiratory management. One intervention which is particularly promising in this population is high flow nasal cannula (HFNC) which has been widely adopted in the pediatric ICU (PICU) setting. Until this past year, HFNC at MGHfC was only administered within the PICU, resulting in increased PICU admissions and potentially reduced access to this therapy outside of this setting. This resulted in reduced efficiency as it required patients that did not necessarily require PICU level of care to occupy PICU beds. This past respiratory season a multidisciplinary team introduced a new clinical pathway to provide HFNC for bronchiolitis patients in the ED and on the pediatric floor. The pathway introduced a standardized scoring system to provide guidance on initiation and maintenance of HFNC, as well as clinical decision making support to determine patients suitable for HFNC on the floor vs the PICU. The goal of this pathway was to expand access to this promising therapy in a safe and consistent way without increasing PICU admissions or length of stay.
Methods: A retrospective data review was conducted over the 5 month period between 11/1/2016-3/31/2017 revealing 102 pediatric admissions to either the MGHfC pediatric floor or PICU with a diagnosis code of bronchiolitis. A similar review was conducted over the period of 11/1/2015-3/31/2016 with 114 admissions over that time period. This second cohort pre-dated implementation of the HFNC clinical pathway and served as a comparator group. Chart review was conducted to assess baseline characteristics, underlying disease, receipt of HFNC, and PICU and floor length of stay.
Results: Incidence of HFNC use following implementation of the clinical pathway increased by 84% (35% vs 19% of admissions, p=0.008) compared to the year prior with 16% of bronchiolitis patients receiving HFNC on the floor at some point during their admission. There was no significant change in average duration of HFNC therapy (3 vs 3.17 days respectively, p=0.66) before and after implementation of the pathway. Additionally, there was no statistically significant difference in the proportion of patients admitted to the PICU (33% vs 30% respectively, p=0.64) or PICU length of stay (3.9 vs 4.8 days, p=0.19). There was no difference in number of patients requiring intubation (4% in each group).
Conclusion: Implementation of a novel clinical pathway at MGHfC to expand access to high flow nasal cannula for bronchiolitis patients resulted in increased utilization of this therapy by 84% without an associated increase in duration of therapy, PICU admissions, or PICU length of stay. Intubation rates were the same in both groups. These findings support implementation of similar pathways to introduce a safe and standardized approach to expanded access to beneficial therapies without an associated increase in resource utilization.

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Alyssa Payette, Anesthesia, Critical Care and Pain Medicine

Tracking Healthcare Worker Competencies and Automated Active Symptom Surveillance for Ebola Virus Disease

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Introduction: During the West African Ebola Virus Disease (EVD) outbreak of 2014-16, health care facilities developing preparedness plans to care for patients with EVD required mechanisms to monitor competencies of healthcare workers (HCWs) and perform monitoring of HCWs for 21 days after last contact in the Biothreats Care Unit (BCU). To address these requirements, a multidisciplinary team at Massachusetts General Hospital (MGH), the Region 1 Ebola and Special Pathogens Treatment Center (RESPTC), developed the Biothreats Tracker Application (BTA).
Methods: The MGH team assessed the requirements of the RESPTC, Occupational Health Services (OHS), and local public health authorities to create an application to monitor competencies of a large team and a mechanism to evaluate HCWs caring for EVD patients. Outcomes assessed included competencies tracked (fit-testing, personal protective equipment training, and

participation in team meetings, drills, and exercises) (Fig.1), BCU entry restrictions based on documented competencies, and deployment of electronic surveys.

Results: BTA tracked the competencies of 166 team members accounting for 314 competency metrics and1,589 training hours in 2016. BTA ensured only trained team members with documented competencies within the prior 90 days were permitted to enter the BCU upon employee badge scan (Fig 2). During 2016, BTA generated 161 surveys; surveys collected feedback from exercises and tested adherence to twice-daily monitoring for clinicians participating in clinical care during exercises.

Conclusion: BTA allowed the RESPTC to successfully track team members, used this information to determine BCU-entry, and surveyed team members electronically. At the time of a BCU activation, BTA allows for real-time competency determination. It is anticipated that electronically delivered twice daily surveys will increase HCW compliance and efficiency of OHS monitoring. This approach can be applied to other highly hazardous communicable diseases for which HCW competencies and active monitoring are required.

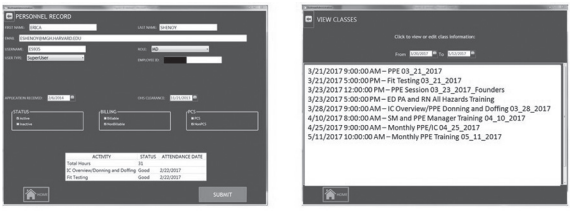

Fig. 1. Tracking Employee Competency and Trainings. The figure above shows the (a) team member personnel record and their competencies that are tracked and (b) the list of scheduled trainings.

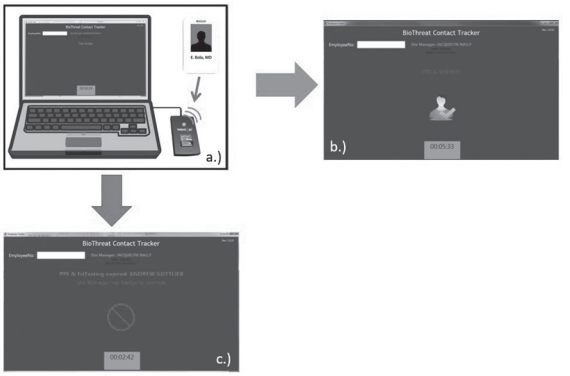

Fig. 2. Admission into the BCU is dictated by completion of training. The figure above shows two scenarios that could occur when a team member taps into the BCU. (a) The user taps their badge on the RFID reader. (b) If they are up to date on training, a green check appears and they can enter. (c) If they are not up to date on training, the system tells you what the user is missing and does not allow them to enter.

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Charles R. Pedlar, PhD, Medicine - Cardiology

Cardiovascular Response to Prescribed Exercise Detraining Among Recreational Marathon Runners

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Introduction: Endurance exercise stimulates numerous changes in cardiovascular structure and function and concomitant increases in blood volume (BV). Exercise induced cardiac remodeling (EICR) is characterized by mild to moderate biventricular eccentric hypertrophy, preserved or enhanced diastolic function, bi-atrial dilation, and BV expansion. EICR has been thoroughly characterized among elite athletes and has recently been documented among recreational athletes who typically perform comparatively lower volumes and intensities of exercise training. Prescribed exercise detraining is proposed as a diagnostic tool for differentiating adaptive EICR from occult cardiomyopathy. However, reference data defining the myocardial response to detraining are limited. We sought to examine the potential reversal of EICR and expanded BV in recreational marathon runners.

Methods: Recreational runners completed a structured 18-week training program (~7 h/w) in preparation for the 2016 Boston Marathon. Following race completion participants reduced total exercise exposure to <2 h/w (no single session >1 hour) for 8 weeks. An overview of the study is displayed in Figure 1. Cardiac structure and function (via echocardiography), maximal treadmill exercise capacity (via integrated cardiopulmonary exercise testing), total haemoglobin mass and blood volume (via carbon monoxide rebreathing) were assessed at peak fitness (10-14 days before) and at 4- and 8-weeks post marathon. Mixed linear modeling adjusting for age, sex, VO_2peak and marathon finish time was used to compare data across time points.

Results: Twenty-one runners (aged 34 ± 7 years; 48% male; see Table 1) completed all aspects of the protocol. Physiologic detraining was evidenced by serial reductions in time to exhaustion during treadmill testing. Two distinct phases of myocardial remodeling and hematologic adaptation were observed. After 4 weeks of detraining, there were significant reductions

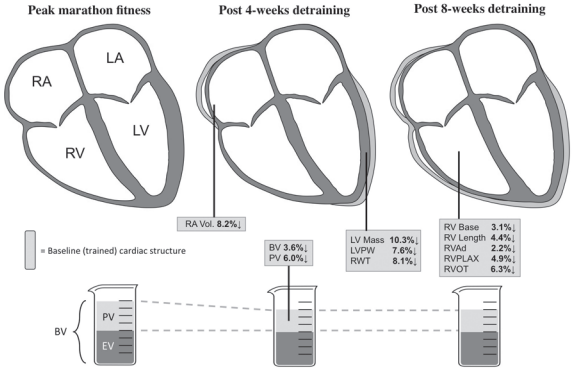
in plasma volume (Δ -6.0%, *P*<0.01), left ventricular (LV) wall thickness (Δ -8.1%, <0.05), LV mass (Δ -10.3%, *P*<0.001), and right atrial area (Δ -8.2%, *P*<0.001). After 8 weeks of detraining, there was a significant reduction in right ventricle chamber size (end-diastolic area Δ = -8.0%, *P* <0.05) without further concomitant reductions in plasma volume or LV wall thickness. See Figure 2.

Conclusion: In conclusion, a sudden decrease in exercise volume for 8 weeks results in the regression of exercise-induced cardiac remodeling and a reduced plasma volume in recreational marathon runners. This regression follows distinct structure-specific 'early' and 'late' time courses characterized by early reductions in LV wall thickness followed by later reductions in RV chamber size. Thus, the duration of prescribed detraining required to differentiate physiologic remodeling from occult cardiomyopathy may vary as a function of the specific cardiac structure in question.

Baseline (at peak fitness) participant characteristics

	All (n=21)	Male (n=10)	Female (n=11)
Age (cms)	32.2 (26.4,38.5)	35.3 (28.7,44.1)	27.6 (26.3,36.9)
Height (cms)	168 (161,174)	175 (172,178)	161 (160,167)
Weight (kgs)	69.7 (57.7,73.3)	73.6 (72.3,79.6)	57.7 (57.1,62.6)
BMI (kg/m^2)	23.1 (21.9,25.8)	24.6 (23.3,26.4)	22.2 (20.9,23.0)
Marathon completion time (hh:mm)	4:21 (4:08,4:51)	4:17 (4:07,4:49)	4:22 (4:10,4:50)
Baseline VO_2peak (ml/kg/min)	48.9 (42.2,54.0)	53.6 (46.4,57.1)	47.9 (40.4,49.8)

Values are presented as median (interquartile range); BMI = Body Mass Index; VO_2peak = Peak oxygen uptake.



The alterations in blood volume and cardiac morphology prior to the Marathon and following 4 and 8 weeks of prescribed detraining. Percentage changes are detailed only where statistically significant. Downward arrow represents reduction. RA = right atrium; LA = left atrium; RV = right ventricle; LV = left ventricle; RVOT = right ventricular outflow tract; BV = blood volume; PV = plasma volume; EV = erythrocyte volume; LVPW = left ventricle posterior wall; RWT = relative wall thickness; RVAd = right ventricle area (diastole); RVPLAX = parasternal long axis view of the right ventricle.

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Sanja Percac-Lima, MD, PhD, Medicine - General Internal Medicine

Lung cancer screening patient navigation for current smokers in community health centers: a randomized controlled trial

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Introduction: Annual chest computed tomography (CT) can decrease lung cancer mortality in high risk individuals. Patient navigation (PN) has been shown to improve cancer screening rates in underserved populations. We evaluated the impact of PN on lung cancer screening (LCS) in current smokers in community health centers (CHC).

Methods: Current smokers aged 55-77 receiving care in five CHC affiliated with Massachusetts General Hospital were randomized to intervention (n=400) or control (n=1200) groups. In the intervention arm, patient navigators (PNs) determined eligibility for LCS, provided brief smoking cessation counseling, introduced shared decision making about LCS, scheduled appointments with the primary care provider (PCP), reminded patients about appointments and PCPs to order CTs, and helped patients attend testing and follow-up any abnormal results. Control patients received usual care. The primary outcome was the proportion of patients in each group who had any chest CT during the study period. Secondary outcomes included proportion of patients receiving lung screening CTs and the number of lung cancers diagnosed in each group.

Results: Baseline patient characteristics were similar between randomized groups. From March 2016-January 2017, PNs contacted 335 (84%) of intervention patients; 76 refused further participation. Of 259 participating patients, 124 (48%) were ineligible for screening: 119 had smoked<30 pack/years and 5 had competing comorbidities. Among 135 eligible participants in the intervention group, 124 (92%) had any chest CT performed. In intention-to-treat analyses, 124 intervention patients (31%) had chest CT vs. 138 control patients (17.3%, p<0.01). Lung cancer screening CTs were performed in 94 intervention patients (23.5%) vs. 69 control patients (8.6%, p<0.01). Eight lung cancers were diagnosed in intervention patients (2%) vs. 4 in controls (0.5%).

Conclusion: A patient navigation program implemented in community health centers significantly increased lung cancer screening among current smokers. Patient navigators may help underserved low-income current smokers complete LCS and improve equity in care while decreasing lung cancer mortality.

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Sarah Phair, MSW, Massachusetts General Physicians Organization (MGPO)

Establishing an MGPO Meaningful Use Incentive Program

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Introduction: In 2011, the Centers for Medicare & Medicaid Services (CMS) implemented the Electronic Health Care Record (EHR) Incentive Program as a means to promote the adoption, implementation, and meaningful use of certified EHR technology by Eligible Professionals (EPs). As defined under the incentive program, commonly known as the EHR Meaningful Use (MU) program, EPs include doctors of medicine or osteopathy, doctors of dental surgery or dental medicine, doctors of podiatry, doctors of optometry and chiropractors. In response to the federal program, the Massachusetts General Physicians Organization (MGPO) established an internal incentive program to personalize the program and promote success among the physicians. The physicians were offered the potential to increase their compensation and improve their skills within the EHR. MGPO resources, such as the MGPO Quality Incentive (QI) program, MGPO staff, and MGPO communications were used to help centralize the program within the MGPO. The QI program was specifically used as leverage to further incentivize and educate physicians as they eased into using the EHR more regularly. The standalone federal MU program is sun setting, but will be rolled under the Merit-Based Incentive Payment System (MIPS). Measures must be met to avoid future payment adjustments. After five years of participation in the federal MU program, the MGPO physicians received over $18.3M in physician incentives, in addition to the support of programs intended to help physicians negate administrative burden (examples include: scribes, Dragon 360, medication transfer, etc).

Methods: The structure of the MGPO MU program was loosely based on the existing MGPO QI program, a unique physician incentive program designed to translate the global performance targets into tangible actions that can be taken by individual physicians. In a couple instances, the QI and MU programs overlapped. A measure relevant to meeting MU standards, such as putting structured fields in the problem lists, was turned into a QI measure. The intention was to encourage physicians to put their "toe in the water" and slowly get used to the measures required by MU. Given the success and recognition of the QI program, the MU measure got more initial traction than if a standalone educational communication had gone out to participating physicians. Initially, the MGPO determined eligibility for the MU incentive based on eligibility for the QI program and if the physician met the federal requirement of being an ambulatory provider. This gave the physician access to MGPO educational resources and the support of MGPO staff to complete the full attestation on the physician's behalf. As the program went on and payment adjustments became more evident, the eligibility pool grew to include MGPO physicians, regardless of their participation in the QI program. The Medicare MU incentive total and the possible payment adjustment was based on Medicare Part B billing. With the MGPO attesting on behalf of physicians, the program had the resources to look into alternative options for attestations. In the last year of attestation, the MGPO used resources similar to the Physician Quality Reporting System (PQRS) reporting, and attested by batch upload. This process eliminated the tedious individual attestations, and allowed for more time to be spend supporting the MGPO physicians.

Results: The MGPO MU program was a successful way to have physicians meet the national standards of the EHR MU program, while also helping the physicians gear up for the transition to Partners eCare (Epic). It boosted physician compensation by providing an additional $3,000 to the annual salary of eligible physicians. The remaining money that was received by the federal program helped support the implementation of Partners eCare (Epic) and MGPO programs intended to reduce administrative burden. While there are no programs on the horizon as lucrative as the federal Meaningful Use program, there were some lessons learned that will be applicable to future incentive programs. For instance, MU is not applicable to all practices. The MPGO wanted to extend the offer to participate to all potentially eligible specialties. While this was first intended as a favor, including them in the potential for a $3,000 annual compensation increase, in many cases, the work needed to meet the full MU requirements ended up being more of a burden to physicians. The biggest area of burden was the patient portal (Patient Gateway) requirements. For example, pediatric patients need to have a parent or guardian connected to the physician through Patient Gateway. This is a fairly easy process if the patient is already a Patient Gateway user. However, it becomes more difficult if they are not, and especially if they are not already a patient in the Partners system. To avoid frustrated physicians, who tried to meet measures not necessarily intended by the federal program to apply to some specialties, communication with the physicians should have been better targeted. Transparency about the likelihood of meeting measures, or complete exclusion from the program, would have been a better option to reduce any additional administrative burden by these physicians. In most cases, the physicians would not have been eligible for any federal payment adjustments. This would end with little risk to not participate. At the end of the five years of MGPO participation, over $18.3M was received by MGPO physicians because of their participation in the MGPO MU incentive program.

Conclusion: The MGPO responded to the EHR Incentive Program and created an MGPO Meaningful Use incentive program. The 5 years of participation in Meaningful Use incentives allowed the MGPO to increase the compensation of our physicians, and prepare them for the transition to Partners eCare (Epic). The additional federal compensation also paved the way for programs helping physicians reduce administrative burden.

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Anne Piantadosi, Neurology

Unbiased pathogen detection in patients with central nervous system infection using metagenomic sequencing

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Introduction: Encephalitis and meningitis are severe neurological syndromes that can result in paralysis, seizures, memory loss, neuropsychiatric sequelae and mortality. Despite extensive testing, nearly 60% of patients with encephalitis remain without clear etiology. To address this challenge, we performed metagenomic sequencing for unbiased pathogen detection among patients enrolled in the Prospective Encephalitis and Meningitis Study (PEMS) at Massachusetts General Hospital. Here, we present the results of metagenomic sequencing from cerebrospinal fluid (CSF) from the first 42 subjects analyzed in this cohort.

Methods: Patients with signs or symptoms of neuro-inflammation without a clear etiology were prospectively enrolled in the PEMS cohort. For metagenomic sequencing, total nucleic acid was extracted from cerebrospinal fluid (CSF), and unbiased sequencing libraries were generated from both RNA and DNA. The RNA portion underwent cDNA synthesis using random primers, and both portions underwent library preparation using Nextera XT (Illumina). Samples were multiplexed along with negative controls (water and/or CSF from uninfected patients from the MGH MIND biorepository) and underwent massively-parallel Illumina sequencing. Reads corresponding to human or known laboratory/background contaminants were removed, and the remaining reads underwent metagenomic analysis using Kraken (Wood *et al. Genome Biology* 2014), as well as a custom database containing all known human pathogens. Clinical details including demographic information, medical history, and clinical lab results were obtained from the REDCap PEMS database, including a chart review performed up to 6 months after discharge. Subjects were classified based on their final clinical diagnosis as "Infectious/Para-infectious", "Autoimmune/Other", and "Unknown." In addition, some patients were enrolled after a known infection was detected by clinical PCR testing from CSF, as positive controls ("Controls"). The Institutional Review Board at MGH approved study protocols, and informed consent was obtained from all subjects.

Results: Clinical characteristics and descriptions of the cohort are summarized in Table 1. Among 42 subjects, 69% were men, and the mean age at presentation was 56 years (SD: 19.5). CSF profiles showed a median pleocytosis of 28 cells/mm3 (range: 0-4175) across the entire cohort, and was highest among Control subjects (120 cells/mm3 [range:22-1875]). Metagenomic sequencing from CSF yielded a median of 2.4 million RNA reads and 8.2 million DNA reads per sample. Among the 15 Infectious/Para-infectious subjects, metagenomic sequencing yielded several interesting findings, including the detection of Powassan virus, an emerging tick-borne flavivirus, in two subjects. In one, we detected Powassan virus by metagenomic sequencing 4 weeks earlier than routine clinical testing by serology, highlighting the potential for this method to provide rapid diagnostic information. In a patient diagnosed with *Anaplasma* by blood PCR, we detected *Anaplasma* in CSF, a compartment not routinely tested because *Anaplasma* has been rarely reported to invade the central nervous system. The Infectious/Para-infectious group included subjects with serology suggestive of recent infection, but negative PCR. In these cases, we did not detect a pathogen by metagenomic sequencing. This included subjects with *Mycoplasma,* varicella-zoster virus, and West Nile virus. The lack of detectable nucleic acid by both clinical PCR testing and metagenomic sequencing suggests that these pathogens may have a short duration of replication in the CSF (if at all) and the clinical syndrome may stem from antibody-mediated or other host-associated factors. Similarly, in one subject diagnosed with Jamestown Canyon virus by serology, we did not detect the virus by metagenomic sequencing in blood and CSF. Very little is known about the pathophysiology of this infection, and our results suggest a short duration of viremia. We did not detect pathogens by metagenomic sequencing in the twelve subjects who do not yet have a definitive clinical diagnosis, or in the eight subjects who were ultimately diagnosed with an autoimmune or other non-infectious syndrome. We detected pathogens in all seven Control subjects, highlighting the ability of our methods to detect both RNA and DNA viruses.

Conclusion: Metagenomic sequencing is a cutting-edge research technique for unbiased pathogen detection that offers promise as a clinical diagnostic strategy to reduce the number of clinical tests required for diagnosis and aid clinicians in rapidly classifying encephalitis and meningitis as infectious versus noninfectious. When applied broadly to subjects with undifferentiated CNS inflammation, metagenomic sequencing identified clinically relevant pathogens, including the locally important Powassan virus and *Anaplasma*. Sequencing from Control subjects also demonstrated the ability to detect both RNA and DNA pathogens in CSF in subjects with known infection, in whom pathogen nucleic acid was also detected by

PCR. However, our results underscore certain limitations of this technique, primarily for para-infectious syndromes in which the clinical presentation may be driven by host responses. The combination of metagenomic sequencing with other platforms such as broad-based antibody detection has the potential to revolutionize CNS infectious disease diagnostics.

Table 1: Cohort Characteristics

	Total (n=42)	Controls (n=7)	Infectious/Parainfectious (n=15)	Autoimmune/Other (n=8)	Unknown (n=12)
Age (yr; mean (sd))	56 (20)	59 (23)	58 (21)	51 (22)	56 (16)
Male Gender (%)	29 (69)	3 (43)	11 (73)	6 (75)	9 (75)
MRI Enhancement (%)	21 (50)	3 (43)	7 (47)	7 (88)	4 (33)
CSF WBC (cell/ul; median [range])	28 [0, 4175]	120 [22, 1875]	38 [4, 191]	2 [1, 140]	22 [0, 4175]
CSF Total Protein (mg/dl; median [range])	68 [15, 930]	93 [39, 930]	78 [17, 197]	50 [15, 212]	72 [28, 196]
CSF Glucose (mg/dl; median [range])	66 [31, 371]	77 [52, 127]	66 [49, 124]	66 [48, 113]	66 [31, 371]
Metagenomic-Identified Pathogen (%)	9 (21)	7 (100)	3 (20)	0	0

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Franziska Plessow, Ph.D., Medicine - Endocrine-Neuroendocrine

Estrogen Status Is Associated with Delay of Gratification in Girls and Young Women with Low-Weight Eating Disorders

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Introduction: Low-weight eating disorders (LWED) frequently onset in adolescence and are characterized by persistent food restriction despite self-starvation. In addition to dietary restraint, individuals with LWED also display an increased ability to delay gratification by means of resisting smaller immediate monetary rewards for larger delayed monetary gains. While this increased delay of gratification to both food and non-food stimuli has been repeatedly discussed as being at the core of the psychopathology of LWED, the potential underlying neurobiological mechanisms are unknown. We hypothesized that estrogen status, known to affect dopamine availability and thereby potentially altering activation in neurocircuitries regulating reward sensitivity and self-regulation, would be associated with delay of gratification in a monetary intertemporal choice task.
Methods: Twenty-seven post-menarcheal girls and young women with LWED (13-21 years; mean±SD: 19.22±2.34 years) completed a well-established monetary intertemporal choice task, in which they had to decide between smaller immediate and larger delayed rewards. For each individual, the extent to which they discounted the monetary value of rewards with increasing delay to delivery (delay discounting) was calculated. Information regarding the number of missed menses over the preceding 0-6, 6-12, and 12-24 months as surrogate marker of estrogen status as well as age at menarche was obtained from their medical history. Body mass index (BMI) Z scores were calculated as a measure of disease severity.
Results: The extent of discounting future monetary rewards was negatively correlated with the number of missed menses in the preceding 0-6 and 6-12 months ($r=-0.58$, $p=0.001$ and $r=-0.55$, $p=0.005$, respectively). The association with the number of missed menses between the preceding 12-24 months did not reach significance ($r=-0.40$, $p=0.057$). The associations between delay discounting and missed menses in the preceding 0-6 as well as 6-12 months remained significant after controlling for BMI Z scores and age at menarche ($p=0.001$ and $p=0.011$, respectively).
Conclusion: The lower the recent estrogen exposure in young females with LWED, indexed as higher number of missed menses in the preceding 0-6 and 6-12 months, the smaller was the extent of discounting the value of monetary rewards over time, and thus the more likely that choices of larger delayed rewards were made over smaller immediate ones (increased delay of gratification). This association strongly indicates the potential involvement of estrogen pathways in the regulation of these behaviors regardless of disease severity and highlights the need for future studies to further investigate their relevance for cognitive-behavioral aspects of LWED psychopathology.

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Haroon S. Popal, Bachelor's, Psychiatry

Altered connectivity of the dorsal attention network in semantic variant Primary Progressive Aphasia

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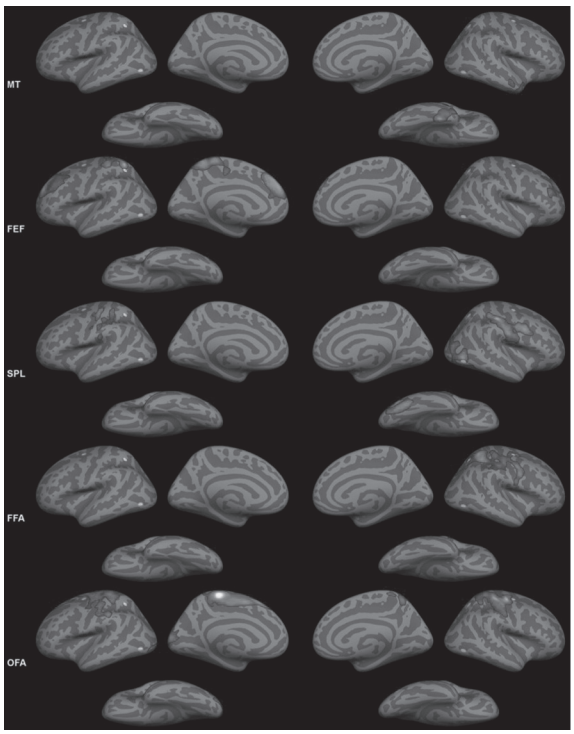
Introduction: Semantic variant Primary Progressive Aphasia (svPPA) is a devastating neurodegenerative disease characterized by the progressive loss of semantic memory and focal atrophy in the left anterior temporal lobe. Strikingly, SD patients also frequently exhibit increased visual interest and repetitive artistic activity. The goal of this study was to investigate whether this heightened visual interest may be due to a reorganization of the functional architecture of the dorsal attention network in these patients.

Methods: We used resting state functional connectivity to investigate the intra- and inter-network connectivity of the dorsal attention network and the ventral visual stream in independent samples of 89 young adult controls (YC), 30 older adult controls, and 12 svPPA patients. Dorsal attention regions of interest included left and right motion-selective cortex (lMT/rMT), frontal eye fields (lFEF/rFEF), and superior parietal lobes (lSPL/rSPL). Left and right fusiform face area (lFFA/rFFA) and left and right occipital face area (lOFA/rOFA) regions of interest were used to investigate connectivity between the ventral stream and the dorsal attention network.

Results: Group level connectivity maps in svPPA patients revealed greater connectivity between ventral stream areas and nodes of the dorsal attention network, particularly with the SPL and FEF seeds, compared to older controls. A whole-brain general linear model analysis replicated these findings, revealing a large cluster in the ventral stream with increased connectivity to the SPL, and a large cluster spanning the SPL and FEF with increased connectivity to the FFA and OFA.

Conclusion: Our results show that nodes of the dorsal attention network have increased functional connectivity with critical regions of the ventral visual stream (the FFA and OFA) in svPPA patients relative to older controls. This altered functional architecture of the dorsal attention network may contribute to heightened visual interest commonly observed in svPPA.



Monte-Carlo corrected general linear model analysis between svPPA and OC groups for each of the ROIs

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Camille E. Powe, M.D., Medicine - Endocrine-Diabetes

The Study of Pregnancy Regulation of INsulin and Glucose (SPRING)

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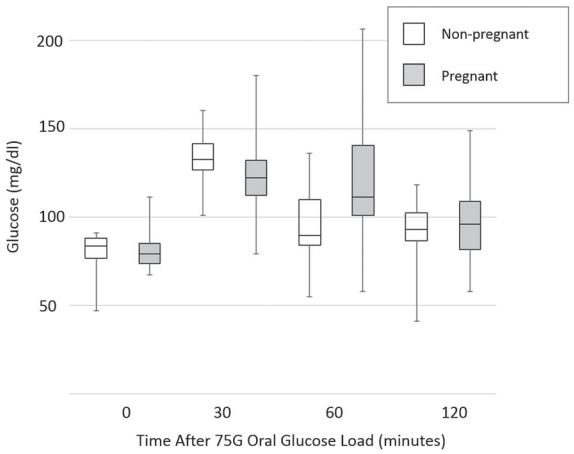
Introduction: Pregnancy leads to profound changes in glucose metabolism, resulting in the development of gestational diabetes mellitus (GDM) in 5-10% of pregnant women. GDM is associated with both perinatal and long term morbidity for mothers and infants. Understanding of the genetic and hormonal determinants of pregnancy glucose metabolism is limited, leading to an incomplete knowledge of the pathophysiology underlying GDM. The Study of Pregnancy Regulation of INsulin and Glucose (SPRING), designed to address these gaps, is a novel longitudinal cohort study of glucose metabolism in pregnancy, based at Massachusetts General Hospital.

Methods: SPRING participants are women, ages 18-44, in the 1st trimester of pregnancy (4-14 weeks gestation). Non-pregnant women are enrolled as control subjects. All participants have risk factors for GDM (for example, GDM in a previous pregnancy, family history of GDM or diabetes mellitus (DM), or body mass index (BMI) ≥ 25 kg/m^2 plus one other DM risk factor). Women with known pre-existing DM, with a hemoglobin A1C ≥ 6.5% at the first study visit, or using medications known to affect glucose metabolism are excluded. At study visit 1 (in the 1st trimester for pregnant subjects), participants complete a questionnaire regarding their medical history, family history, obstetric history, lifestyle, and demographics. Participants then undergo a fasting two-hour 75-gram oral glucose tolerance test (OGTT) with blood sampling at baseline, 30 minutes, 60 minutes, and 120 minutes for glucose and insulin levels. Whole blood samples are collected for Hemoglobin A1C and DNA extraction. Additional urine, serum, and plasma samples are frozen and stored for future analyses. Pregnant participants will be followed longitudinally during pregnancy. In this preliminary analysis, we compared characteristics of the pregnant and non-pregnant subjects recruited thus far into our cohort. Using the OGTT glucose and insulin levels, the Matsuda index and Insulinogenic Index were calculated to estimate insulin sensitivity and early insulin secretion in response to a glucose load, respectively. Continuous variables were compared using Wilcoxon Rank-Sum tests and categorical variables were compared using the chi-squared test or Fisher's exact test, as appropriate. Statistical analyses were conducted in STATA version 14 (StataCorp, College Station, TX).

Results: Forty-seven subjects, 32 pregnant and 15 non-pregnant, enrolled in SPRING and had data available at the time of the present analysis. Compared to pregnant subjects, non-pregnant subjects were younger (median [IQR] age 26 [24.5-28] years versus 32 [29.5-34.25] years, *P*=0.01) and more likely to be nulliparous (86.67% versus 50.00%, *P*=0.02). Other subject characteristics including BMI, family history of diabetes, and race/ethnicity were similar between the two groups. Racial and ethnic minorities comprised 55.3% of subjects enrolled. The median [IQR] gestational age of pregnant subjects was 12.5 [12.0-13.5] weeks at the time of study. Among subjects with complete laboratory data at the time of analysis (n=33), there were no statistically significant differences in glucose and insulin levels at OGTT timepoints between pregnant and non-pregnant women, though pregnant women appeared to have higher 60-minute glucose levels than non-pregnant women (111 [101-140.5] versus 89.5 [84-109.75] mg/dl, *P*=0.08, Figure 1). Insulin levels at all time points were similar between the 2 groups, as were measures of insulin sensitivity and early insulin secretion in response to the glucose load.

Conclusion: SPRING is an ongoing longitudinal cohort study of glucose metabolism in pregnant women. Enrolled non-pregnant control subjects are younger and more likely to be nulliparous, but are otherwise similar to pregnant subjects in terms of body mass index, race/ethnicity, and family history. Preliminary analyses suggest that glucose metabolism in 1st trimester pregnant women is not dramatically altered from the non-pregnant state, though 60 minute glucose levels appeared higher in pregnant women. Future analyses will perform the same comparisons in a larger number of women, incorporate genomic data, and examine changes in glucose metabolism across pregnancy and postpartum.



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Jacqueline Proszynski, B.S., Psychiatry - Benson Henry Institute for Mind Body Medicine

Correlates of Practice Adherence in Mind-Body Medicine Interventions

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Introduction: Mind-body interventions aim to improve health and wellbeing by reducing stress and increasing resilience. However, an individual's expectations for treatment efficacy may influence the time and effort invested in an intervention. We hypothesized that participants who reported higher positive expectations for a stress management intervention would be more likely to adhere to intervention attendance and at-home practice.

Methods: Adults reporting six months of moderate to severe chronic stress were randomized into one of three 8-week stress management interventions: yoga, meditation or stress education. The Expectancy Questionnaire was administered at baseline prior to intervention start. For each intervention, subjects attended once weekly individual trainings and completed a 20-minute daily at-home practice. Practice hours were recorded in a daily electronic diary entry. Adherence was measured by number of intervention sessions attended, total reported at-home practice sessions, and total reported at-home practice (in minutes) during the intervention and in the 4-month follow-up period after intervention completion.

Results: 179 participants (mean age = 35 ± 13.87) were included in the analyses. Contrary to our hypothesis, Pearson's correlations showed that expectancy for the program to reduce stress was not associated with attendance (r=0.09), the number of at-home practice sessions (r=0.008) or total number of at home practice hours (r=0.009). However, moderate correlations were found between number of sessions attended and number of at-home practice sessions (r=0.47) and total practice hours (r=0.46). This relationship continued, although weakly, during the follow-up period (r=0.31 and 0.32, respectively).

Conclusion: Expectation for the intervention to reduce stress did not correlate with study adherence; however, given the moderate relationship between attendance and at-home practice behaviors, session attendance may serve as a marker of participant conscientiousness or buy-in. Alternatively, higher intervention attendance may influence comfort with and/or confidence in, and thus probability of, practicing at home.

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Elaina Pullano, Oral and Maxillofacial Surgery

Does the medical comorbidity profile of OSA patients treated with maxillomandibular advancement differ from that of OSA patients managed nonsurgically?

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Introduction: To describe and compare the comorbidity profiles of of obstructive sleep apnea (OSA) patients managed surgically with maxillomandibular advancement (MMA) to those of OSA patients managed nonsurgically.
Methods: Subjects for both cohorts were identified through the Oral and Maxillofacial Surgery (OMFS) data registry and the MGH Research Patient Data Registry (RPDR). Inclusion criteria consisted of clinical records documenting BMI, AHI, RDI, and/or O_2 nadir. The primary predictor variable was the treatment modality chosen: surgical (MMA) or nonsurgical. The primary outcome variables were those comorbidities reported to be associated with OSA. Demographics and secondary outcome variables were also evaluated.
Results: The surgical cohort consisted of 51 individuals (84.3% male) and the nonsurgical cohort consisted of 71 (67.6% male), all of whom met inclusion criteria. Comparison of descriptive characteristics showed that the nonsurgical cohort had a higher average age (49±9.4) than the surgical cohort (41±10.7; P< .001). A higher average BMI was also present among the nonsurgical group (42.3±11.9 nonsurgical vs. 29.7±5.5 surgical; P<.001). Polysomnogram parameters were found to be comparable except for a higher ESS in the surgical cohort (15.5±5.30 surgical vs. 9.90±6.80 nonsurgical; P=.005). The nonsurgical cohort had a higher total number of comorbidities (7± 4 nonsurgical vs. 4± 3 surgical; P<.001). Specific comorbidities found to have a higher prevalence among the nonsurgical group include hypertension, cardiovascular disease, hyperlipidemia, pulmonary hypertension, obstructive pulmonary disease, and type 2 diabetes.
Conclusion: The results of this study suggest that nonsurgically managed OSA patients tend to have more complex medical comorbidity profiles than those managed surgically. Morbid obesity was additionally prevalent in the nonsurgical cohort, which may contribute to these findings. The additive contribution of OSA in these patients still needs to be elucidated.

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Alexa Pulli, BS, Psychiatry

Does the Mixed Opiod Recepter Antagonist Naltrexone Mitigate Stimulant-Induced Euphoria?: A Double-Blind, Placebo Controlled Trial of Naltrexone

T.J. Spencer[1,3], P. Bhide[2], A. Pulli[1], M. Fitzgerald[1], A. Yule[1,3], M. Uchida[1,3], B. Storch[1] and J. Biederman[1,3]

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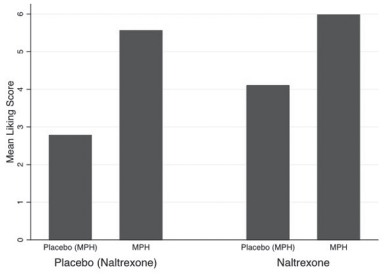
Introduction: Supra therapeutic doses of methylphenidate (MPH) activate mu opioid receptors, which are linked to euphoria. This study assessed whether naltrexone, a mixed mu opioid antagonist, may attenuate the euphoric effects of stimulants, thereby minimizing their abuse potential in subjects with Attention Deficit Hyperactivity Disorder (ADHD).
Methods: We conducted a six-week, double-blind, placebo-controlled, randomized clinical trial of naltrexone in adults with DSM-IV ADHD receiving open treatment with a long acting formulation of MPH (January 2013 to June 2015). Spheroidal Oral Drug Absorption System (SODAS)–MPH was administered BID and titrated to ~1 mg/kg/day over three weeks and continued for three additional weeks depending on response and adverse effects. Subjects were adults with ADHD preselected for having experienced euphoria with an oral test dose of 60 mg of immediate release (IR) MPH. The primary outcome measure was Question 2 (liking) on the Drug Rating Questionnaire (DRQ-S) after additional oral test doses of 60 mg of IR-MPH at the 3rd and 6th week of treatment with SODAS-MPH.
Results: Thirty-seven subjects who experienced stimulant-induced (mild) euphoria on a baseline visit were started in the open trial of SODAS-MPH and randomized to 50 mg naltrexone or placebo. Thirty-one subjects completed through Week 3, twenty-five through Week 6. Naltrexone significantly diminished the euphoric effect of IR-MPH during the titration phase (first three weeks) but not the stabilization phase (Weeks 4 to 6) of SODAS-MPH treatment.
Conclusion: These findings extend to humans preclinical findings showing that naltrexone may mitigate stimulant-associated euphoria. Our findings provide support for the concept of combining opioid receptor antagonists with stimulants to provide an effective stimulant formulation with less abuse potential.

Figure 2a. Poisson regression model predicting liking a drug effect at Week 3 controlling for baseline euphoria: the MPH x naltrexone interaction (N=31).



*There is a significant interaction between MPH and naltrexone (p=0.02).

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Katharine M. Quain, B.S., Psychiatry

Quality of Life and Psychological Distress in Patients with Malignant Gliomas and Their Caregivers

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Introduction: Patients with malignant gliomas have a poor prognosis and high symptom burden. The supportive care needs of this population and their families have not been well described. We evaluated depression, anxiety, and quality of life in patients with malignant gliomas and their caregivers.

Methods: We conducted a longitudinal study in patients with newly diagnosed malignant gliomas and their caregivers, collecting self-report data at diagnosis and at 3, 6, and 9 months post-diagnosis. Depression and anxiety symptoms were assessed by the Hospital Anxiety and Depression Scale, with subscale scores >7 considered clinically significant. Health-related quality of life was evaluated by the Functional Assessment of Cancer Therapy - Brain Cancer (FACT-Br), with higher total scores corresponding to better quality of life. We calculated an independent samples t-test to evaluate differences in quality of life between patients with versus without clinically significant depression or anxiety symptoms at baseline.

Results: 35.7% (25/70) of patients and 75.4% (43/57) of caregivers were women, and the average age was 56.5 years old for patients and 54.4 years old for caregivers. 77.2% of caregivers were spouses of patients (44/57) and a majority lived in the same residence as the patient (82.5%, 47/57). 24.3% (17/70) of patients and 54.4% (31/57) of caregivers experienced clinically significant anxiety symptoms at diagnosis. Additionally, 22.9% (16/70) of patients and 26.3% (15/57) of caregivers experienced significant depression symptoms. Rates of caregiver anxiety remained high over time, with more than 60% of caregivers reporting clinically significant anxiety symptoms at 6 and 9 months post-diagnosis. Patients who reported elevated depression or anxiety symptoms at baseline had lower health-related quality of life at diagnosis (M=127.4, SD=25.6) compared to patients without clinically significant depression or anxiety symptoms (M=156.1, SD=20.3), $t(68) = -5.125$, $p<0.001$.

Conclusion: A significant proportion of patients with malignant gliomas have psychological distress at the time of diagnosis. Their caregivers experience even higher rates of psychological distress, with the majority reporting anxiety throughout the patients' illness course. Patients with baseline depression or anxiety symptoms also experienced lower health-related quality of life at diagnosis. Interventions are needed to provide psychosocial support for these patients and caregivers.

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Aaishah R. Raquib, Massachusetts Eye and Ear Infirmary (MEEI) - Otolaryngology

Endoscopic Management of Lateral Sphenoid Cerebrospinal Fluid Leaks

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Introduction: With advances in endoscopic technology, the endonasal endoscopic approach has become the gold standard in the repair of cerebrospinal fluid (CSF) leaks, with success rates greater than 90%.[1,2] CSF leaks originating in the sphenoid sinus pose an operative management challenge due to the proximity to critical structures, such as the carotid artery, cavernous sinus, and optic nerve.[3] CSF leaks can occur from the planum sphenoidale, perisellar area, or the lateral recess.[4,5]

Woodworth et al. found that the lateral sphenoid sinus was the most common area for spontaneous CSF leaks, occurring in 35% of spontaneous CSF leaks. The lateral recess of the sphenoid (LRS) is described as the area lateral to the vidian to foramen rotundum line (V-R line) in a pneumatized portion of the pterygoid process.[5–8] CSF leaks in this area are difficult to access by the transnasal endoscopic approach because of limitations with lateral maneuverability.[9] Previous reports have described utilization of the endoscopic endonasal transpterygoid (EETP) approach for defects within the LRS.[5,10–12] This approach allows direct exposure of the defect through total or partial removal of the pterygoid process.[10,13,14] Herein, we review our experience with surgical repair of CSF leaks within the LRS over the last 12 years. Radiographic measurements were reviewed to create an algorithm to determine the appropriate endoscopic approach necessary for exposure and repair.
Methods: A retrospective chart review was performed on patients diagnosed with sphenoid CSF leaks repaired at Massachusetts Eye and Ear Infirmary between 2004 and 2016. Clinical information including, age, sex, history of previous surgery, presenting symptom, CSF leak etiology, location of intrasphenoidal skull base defect, presence of encephalocele, surgical approach of repair, type of graft, and follow-up evaluation were obtained from clinical notes, operative reports, and preoperative radiographic studies. Measurements of the V-R line were obtained from preoperative radiographic studies. Patients lost to follow-up or without radiographic imaging were excluded.
Results: Forty-seven CSF leaks originating in the sphenoid sinus were repaired in 39 patients over the 12 year period. Of these, 19 (40.4%) of CSF leaks occurred from the LRS in 16 patients. There were 5 male patients and 11 female patients, with a median age of 53.0 years (range, 35-67 years). The median duration of follow-up was 11 months (range, 1-68 months). There was a 89.5% success rate on the first attempt. Two patients suffered from recurrent CSF leak on the contralateral side. The etiology of the CSF leaks was spontaneous in 16 of the repairs and traumatic in 3 cases. Meningocele or meningoencephalocele was present in 12 (63.2%) of the LRS defects. The transnasal approach was used in 5 (26.3%) of the LRS skull base repairs and the EETP approach was used in 14 (73.7%) of the CSF leaks. Thirteen defects were repaired with a free mucosal graft, 2 with vascularized graft, 3 with fascia, and 2 with alloderm. Rigid support with bone or cartilage was used in 14 of the repairs. All but one of the 14 LRS CSF leak repairs accessed by the EETP approach had a V-R angle less than 46.6 degrees (median 33.2 degrees, range 10.8-49.8 degrees). The 5 LRS CSF leak repairs accessed transnasally had a V-R angle above 46.7 (median 47.3 degrees; range 47.2-59.2 degrees).
Conclusion: CSF leaks originating in the LRS are most commonly spontaneous in etiology and most require the endoscopic endonasal transpterygoid approach for adequate access. The angle of the V-R line can provide a guideline in presurgical planning of LRS CSF leaks. Wide exposure with the EETP approach with multilayered closure with rigid support provides 89.5% success rate in the repair of LRS CSF leaks.

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Revathi Ravi, MD, Emergency

Feasibility of an innovative, low-cost, best-evidence bubble Continuous Positive Airway Pressure (CPAP) package with pulse oximetry in Kenya and India

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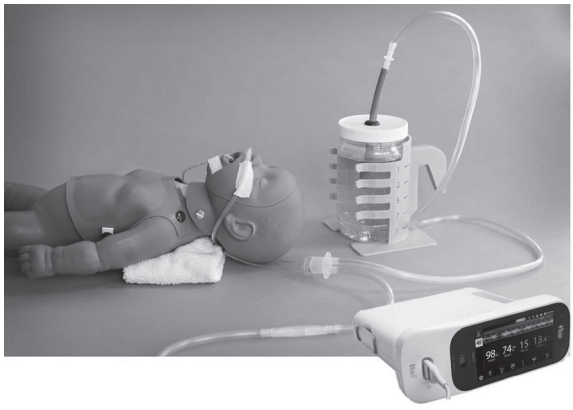
Introduction: Acute respiratory distress leading to respiratory failure is a leading cause of death in children worldwide. Ninety-nine percent of deaths in children under 5 years occur in low- and middle-income countries. The leading causes are prematurity, sepsis, and pneumonia, with respiratory compromise occurring in all three. In resource-limited settings where the burden of newborn death and disease is highest and access to advanced airway management low or inaccessible, early identification and management of respiratory distress is critical to reducing newborn deaths. The aim of this study was to determine the feasibility of an innovative, low-cost, best-evidence, all-inclusive bubble CPAP package for newborns called Every Second Matters – Newborn Respiratory Bundle (ESM-NRB)^{TM} in Kenya and India. ESM-NRB is aimed at providing advanced pediatric respiratory support using a low-cost, innovative bubble CPAP device, hospital-grade pulse-oximeter, and complete training package aimed at low-resource settings.
Methods: The ESM-NRB^{TM} package includes a best evidence bubble CPAP kit, hospital grade pulse oximeter, clinical pathway, safety checklist, training manual, and two-day intensive training including both didactic and practical application for newborns up to 3 months of age. The bubble CPAP kit uses an oxygen source – rather than an electricity-requiring pump – to provide continuous positive airway pressure. Oxygen is funneled through a low-cost innovative blender which provides a fixed fraction of inspired oxygen (FiO_2) and is bubbled under water to create pressure within the system. The depth below

the surface of the water in centimeters determines the pressure. Continuous airway pressure is delivered via adaptable nasal prongs which, through an innovative sponge adaptation, create a closed-pressure system. The ESM-NRB^{TM} clinical pathway includes a set of inclusion criteria with initiation of treatment measures; well-defined gastrointestinal, anatomical, respiratory, cardiovascular, and neurological exclusion criteria; vital sign assessment; respiratory severity assessment; and monitoring for signs of improving or worsening respiratory status based on signs and symptoms of respiratory distress. The ESM-NRB^{TM} safety checklist provides a step-by-step methodology to safely apply and use bCPAP. Providers undergo a two-day intensive training reviewing the physiology and clinical aspects of respiratory distress, set-up, and application of the low-cost innovative bubble CPAP device, and risk and evaluation of newborns on bubble CPAP. Providers use the clinical pathway and safety checklist to ensure proper setup, application, and safety of the newborn. Clinical scenarios are used for practical implementation. Following practical training, providers spend time within their own hospitals and other low-resource settings, identifying newborns in respiratory distress, those who could benefit from bubble CPAP application, and application of ESM-NRB^{TM} to those who meet criteria in accordance with the clinical pathway. Physicians, clinical officers, nurses, and residents from ten hospitals across Kenya and India completed the two-day intensive training. These clinical providers implemented ESM-NRB^{TM} within their own facility. Data were collected prospectively each time ESM-NRB^{TM} was applied through a series of data collection cards which examined the full clinical record, included continuous safety monitoring, and an assessment of patient outcomes once bCPAP was no longer being used. The clinical course and outcomes of all patients supported with ESM-NRB^{TM} were analyzed.

Results: Between May 26, 2017 and July 31, 2017, the ESM-NRB^{TM} package was used to provide respiratory support to 29 newborns – 7 in Kenya and 22 in India. Among the 29 cases, 16 (55.17%) were preterm with the youngest at 27 weeks gestation and a weight of 700g. Respiratory rate at time of implementation for all 29 cases ranged from 58 to 110 breaths per minute and at the time of removal were down to 20 to 88 breaths per minute. Average length of time on bubble CPAP was 35.75 hours, ranging from 15 minutes to 240 hours. Respiratory severity scores at time of device application ranged from 2 to 9, and at time of removal ranged from 0 to 8. Among the 29 cases, 8 (27.59%) were diagnosed with respiratory distress syndrome, 1 (3.45%) with pneumonia, 16 (55.17%) with prematurity, 3 (10.35%) with meconium aspiration syndrome, and 6 (20.69%) with transient tachypnea of the newborn. After implementation of ESM-NRB^{TM}, 26 (89.65%) were successfully weaned to room air, and 1 (3.45%) was transferred and intubated. The survival rate across both countries of newborns supported by ESM-NRB^{TM} is 93.1%.

Conclusion: The ESM-NRB^{TM} package can be feasibly implemented in resource-limited settings for the support and care of a wide range of diagnoses that include respiratory distress and compromise in newborns.



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Molly Ream, Psychiatry

Patient Engagement with a Smartphone Mobile App for Adherence to Orally Administered Cancer Therapy

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Introduction: Over the last decade, orally administered cancer therapy medications have become available for treatment of a wide range of malignancies. Patients prescribed oral therapy generally receive minimal supervision and support for adherence and monitoring of side effects as opposed to directly-observed infusion chemotherapy. We developed a Smartphone mobile application (app) designed to improve adherence and symptom management for patients with a diverse range of malignancies prescribed oral therapy. In this study, we sought to describe overall app engagement and identify potential correlates of app usage.

Methods: From 12/2014 to 08/2016, 181 patients with diverse malignancies prescribed orally administered cancer therapy, either oral targeted therapy or oral chemotherapy, enrolled in a randomized trial to test the efficacy of a Smartphone mobile app to improve adherence and symptoms. We developed the comprehensive mobile app by incorporating feedback from focus groups with key stakeholders, including patients and family members, oncology clinicians, healthcare representatives, and practice administrators. We conducted extensive user testing to refine the app to improve usability and feasibility. The final mobile app, Chemotherapy Assistant (CORA), included a medication treatment plan, medication reminders, symptom reporting and review, educational resources for managing symptoms, exercise monitoring device, free notes section, and weekly adherence reporting. Data on self-reported symptom severity and adherence was sent weekly to the oncology team via HIPAA-compliant email. Patients randomized to the intervention group used the app on their personal Smartphones for 12 weeks. In addition to self-report, medication adherence was monitored using electronic pill caps (MEMScaps). At baseline (pre) and 12 weeks (post), participants completed a measure of satisfaction with clinician communication and treatment (Functional Assessment of Chronic Illness Therapy - Treatment Satisfaction). Through the app we collected data on engagement: total number of minutes, days of usage, and number of completed symptom reports. We calculated Pearson correlations to identify associations between app engagement, using a latent variable representing overall engagement, with adherence, treatment satisfaction and healthcare utilization.

Results: 91 patients were randomly assigned to receive the mobile app. Patients' mean age was 52.85 years (SD=13.74), approximately half were female (50.5%), and the majority were Caucasian (92.3%). All patients were prescribed either oral targeted therapy (71.4%) or oral chemotherapy (28.6%) for their cancer treatment. Over the 12-week study period, participants used the mobile app for a mean of 59 minutes (SD=68) and 21.75 discrete days (SD=21.24 days), completing an average of 15.92 symptom reports (SD=14.15). The medication treatment plan timeline was the most frequently visited page of the app, followed by the educational library, the symptom graph review, the ad-hoc symptom reporting module, and the free notes section. Higher app engagement was associated with having a lower proportion of missed doses (r=-.248, p=.035) over the study period. Patients who became less satisfied with their communication with physicians (r=-.278, p=.019) and nurses (r=-.238, p=.047) from baseline to 12 weeks used the app more. Higher app engagement was associated with fewer emergency department visits resulting in hospitalizations during the study period (r=-.252, p=.029).

Conclusion: Overall, patients prescribed orally administered cancer therapy used the app features that were intended to improve adherence and symptom management. The symptom module was heavily utilized to report and monitor symptoms. Higher usage of the mobile app was related to fewer missed doses and ED visits leading to hospitalization. Fostering patient engagement with the app may also serve to buffer difficulties in patient-clinician communication about care. These data suggest the potential value of maximizing patient engagement with a mobile app.

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Balaji Reddy, MD, Urology

Mortality related to the use of stapler device and clip appliers: Analysis of the FDA MAUDE database.

B. Reddy[1], A. Nehra[1], A. Singla[1], M. Subhash[3], M. Vangel[2], M. Blute[1] and M. Wszolek[1]

[1]Urology, Massachusetts General Hospital, Boston, MA, USA, [2]Biostatistics, Massachusetts General Hospital, Boston, MA, USA and [3]Obstetrics and Gynecology, Tufts Medical Center, Boston, MA, USA

Introduction: Stapling devices and clip appliers are commonly used in surgical procedures. They are known to malfunction, which may result in serious injury, or death. We characterized the adverse outcomes related to the malfunction of Stapling devices or clip appliers, and the clinical implications of such events using the FDA MAUDE database.

Methods: We reviewed the FDA MAUDE database between 2007 and 2016 using the following product codes: GAG (surgical staplers), FZP (implantable clip), GDO (surgical clip appliers), and GDW (implantable staple). The detailed reports and the device problem for each reported event were reviewed to determine the clinical implications. A correlation analysis was performed between the adverse events and the device recall. A random-effects logistic regression model was used to predict injury and death based on the malfunction. Statistical analysis was performed using R.

Results: Between 2007 and 2016, 94 deaths were related to the use of stapler and clip applier devices. Most deaths occurred post-operatively (N=71, 75.5%). Intra-operative mortality was related to vascular injuries (100%); postoperative mortality was related to infection or sepsis (N=49, 69%) and vascular injuries (N= 22, 31%). Device failure was noted both intra-operatively (N=40, 42.6%) and post operatively (N=49, 52.1%). Among those with an intra-operative recognition of device failure, 13 (32.5%) died intra-operatively, and 21 (52.5%) died postoperatively. The device problem codes associated with these devices showed a device problem in 62%, no known device problem identified in 29%, and attributed to improper operator use in 4%. We found significant correlation between serious injury and death (Spearman correlation co-efficient 0.654, p=0.04) as well as malfunction and serious injury (Spearman correlation co-efficient 0.648, p=0.04). The probability of injury given malfunction is 0.19 (SE 0.12); the probability of death given malfunction is 0.011 (SE 0.008).

Conclusion: Device malfunction predicts serious injury and death. Improvement to the design of surgical staplers and clip appliers has a role in reducing device related mortality. Additionally, surgeons must anticipate device related adverse events in optimizing patient outcomes.

Table 1: Stapling device and clip applier related death:

Type of Surgery	
Gastrointestinal	42 (44.7%)
Cardio-thoracic	27 (28.7%)
Hepatic, Kidney or Spleen	19 (20.2%)
ENT	2 (2.1%)
Not reported	4 (4.3%)
Time of device failure recognition	
Postoperative	49 (52.1 %)
Intra-operative	40 (42.6%)
Not reported	5 (5.3%)
Time of death	
Post-operative mortality	71 (75.5%)
Intra-operative mortality	13 (13.8%)
Not reported	10 (10.6%)

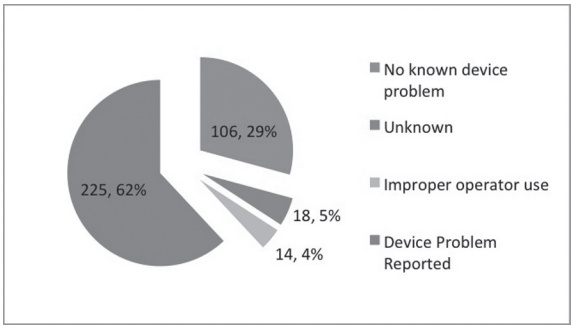

Figure 1: A breakdown of the device problem (N, %)

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Krishna P. Reddy, Medicine - Pulmonary

Lung Cancer Mortality among People Living with HIV in the United States: Impact of Smoking and Smoking Cessation

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Introduction: People living with HIV (PLWH) in the US face a high risk of lung cancer, both because >40% of PLWH smoke cigarettes and because HIV is an independent risk factor for lung cancer. Lung cancer has become a leading cause of death among PLWH in the US. We sought to project the cumulative lung cancer mortality by smoking exposure, and the number of lung cancer deaths expected, among PLWH in care in the US.

Methods: We used a validated Monte Carlo microsimulation model of HIV disease and treatment to project cumulative lung cancer mortality by age 80 among PLWH in care in the US according to age, sex, and smoking exposure, combining smoking status (current, former, or never) and intensity (heavy, moderate, or light, based on cigarettes per day). We stratified reported mortality rates attributable to lung cancer and to other non-AIDS-related causes by smoking exposure, and we accounted for an HIV-conferred independent risk of lung cancer (rate ratio 1.7, versus HIV-uninfected people). Lung cancer mortality risk ratios (versus never smokers) for male/female current moderate smokers were 23.6/24.2, and for those who quit at age 40 were 4.3/4.5. In sensitivity analysis, we accounted for non-adherence to antiretroviral therapy (ART), and for a range of HIV-conferred risks of death from lung cancer and from other non-AIDS-related diseases (e.g., cardiovascular disease). Additionally, we estimated the number of lung cancer deaths by age 80 if smoking habits did not change among PLWH aged 20-64 in care in the US (accounting for reported rates of non-adherence to ART), and the potential reduction in lung cancer deaths if 20% of current smokers in HIV care quit smoking and remained abstinent.
Results: Among 40 year-old men with HIV, estimated cumulative lung cancer mortality for heavy/moderate/light smokers who continued to smoke was 28.9%/23.0%/18.8%, for those who quit smoking at age 40 was 7.9%/6.1%/4.3%, and for never smokers was 1.6%. Among women, the corresponding mortality for current smokers was 27.8%/20.9%/16.6%, for former smokers was 7.5%/5.2%/3.7%, and for never smokers was 1.2%. ART-adherent individuals who continued to smoke were 6-13 times more likely to die from lung cancer than from traditional AIDS-related causes, depending on sex and smoking intensity. For 40 year-old ART-adherent men who were current moderate smokers, the combined cumulative mortality from lung cancer and other non-AIDS-related causes – both of which were increased by smoking – was approximately 35 times that from AIDS-related causes; for women, it was approximately 27 times higher (Figure, Panels A-C). Due to greater AIDS-related mortality risks, individuals with incomplete ART adherence had higher overall mortality but lower lung cancer mortality (Figure, Panels D-F). Applying model projections to the ~644,200 PLWH aged 20-64 in care in the US (both smokers and non-smokers), 59,900 (9.3%) are expected to die from lung cancer if smoking habits do not change.
Conclusion: PLWH who adhere to ART but smoke are substantially more likely to die from lung cancer than from AIDS-related causes. Even when accounting for non-adherence to ART, nearly 1 in 10 PLWH initially linked to care in the US (combining both smokers and non-smokers) are expected to die from lung cancer if smoking habits do not change. Smoking cessation should be a priority in the care of PLWH.

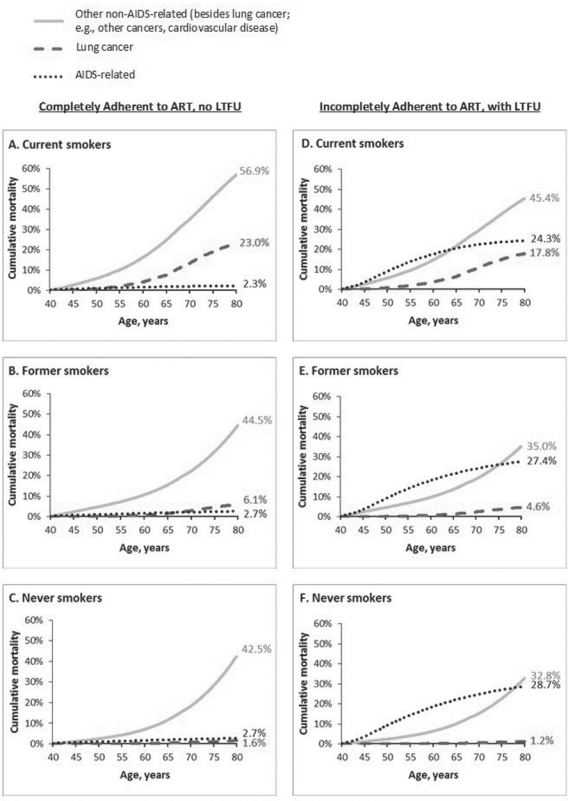

Figure. Cumulative Mortality by Cause among Men Entering HIV Care at Age 40. ART: antiretroviral therapy; LTFU: loss to follow-up. Panels A-C reflect simulations of men who are completely adherent to ART and are never lost to follow-up from HIV care. Panels D-F reflect simulations incorporating reported rates of non-adherence to ART and loss to follow-up from HIV care. Panels A and D depict current smokers, Panels B and E depict former smokers, and Panels C and F depict never smokers. The intensity of smoking (cigarettes per day) for current and former smokers was considered to be moderate ("average"). Current smokers continued smoking until the end of follow-up. Former smokers quit at age 40 and remained abstinent. Deaths from non-AIDS-related causes besides lung cancer are depicted by the solid blue lines, deaths from lung cancer are depicted by the dashed red lines, and deaths from AIDS-related causes are depicted by the dotted black lines.

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Beverly Reynolds, Neurology

[^{18}F]-GE180 Compared to [^{11}C]-PBR28 in Detecting In Vivo Glial Activiation in People with ALS

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Introduction: [^{18}F]-GE180 and [^{11}C]-PBR28 are different radiotracers that both bind to translocator protein (TSPO), which is expressed on reactive glial cells. People with ALS show increased [^{11}C]-PBR28 uptake in the motor cortices that is highly correlated with clinical phenotype [1,2]. [^{18}F]-GE180 has a longer half-life than [^{11}C]-PBR28, which could allow for radiolabeling and distribution from regional radio pharmacies to facilitate multicenter studies. This is the first study to use [^{18}F]-GE180 PET imaging in people with ALS. The primary objective of this project is to compare radiotracer uptake in the motor cortices in people with ALS imaged with both [^{18}F]-GE180 and [^{11}C]-PBR28 positron emission tomography (PET).
Methods: Eight ALS participants and eight HC underwent [^{18}F]-GE180 PET scans. Six of those participants (five ALS and one HC) were also scanned using [^{11}C]-PBR28 PET within one month of the [^{18}F]-GE180 PET scan. PET images were acquired 60-90 minutes after radiotracer injection, and the standardized uptake value ratio (SUVR) normalized to whole brain was used to quantify the tracers' s uptake in the brain. A composite region of interest (ROI) has been formed from the precentral gyri bilaterally and its continuation on the medial surface of the hemisphere (i.e. the paracentral gyrus). SUVR-GE180 and SUVR-[^{11}C]-PBR28 were compared between ALS and HC within the ROI.

Results: The signal captured by [^{11}C]-PBR28 PET in the motor cortices of people with ALS was higher and more informative than [^{18}F]-GE180 PET. In the ROI, the mean [SD] of SUVR-[^{11}C]-PBR28 in five ALS participants was 1.05 [0.042], while the mean [SD] of SUVR-GE180 in the same five ALS participants was significantly lower (0.96 [0.031]; P<0.05). A comparison in SUVR-GE180 between eight ALS individuals, and eight HC within the ROI revealed no difference between the groups (HC: 0.95±0.09; ALS: 0.96±0.03; P=0.67).
Conclusion: [^{18}F]-GE180 PET is not as sensitive as [^{11}C]-PBR28 PET in imaging glial activation in people with ALS.

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Kerry L. Reynolds, MD, Medicine - MGH Cancer Center

A Tsunami Is Coming: Rapid increase in inpatient admissions for immune-related adverse effects (irAE) among patients treated with immune checkpoint inhibitors for advanced malignancy.

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Introduction: Immune checkpoint inhibitors are currently in clinical trials for a wide range of malignancies. Over the last six years there has been an increase in the number of FDA approvals for immune checkpoint inhibitors. They work to harness the immune system to attack cancer, and have dramatically changed the landscape of available treatments in the past decade. Immune modulation is a rapidly expanding field with clinical trials studying combinations of approved and experimental immunotherapies. In a minority of patients, these agents are associated with significant response rates in malignancies with historically poor prognoses (metastatic melanoma, bladder cancer, non-small cell lung cancer, and others), and these responses may be durable for years. Unfortunately, such treatment comes with the potential for serious toxicity. Disruption of the immune system with immune checkpoint inhibitors can result in a multitude of immune-related adverse effects (irAE) in any organ or gland. irAEs are graded according to their severity by the Common Terminology Criteria for Adverse Events (CTCAE), and some are life threatening. High-grade toxicities (grade 3 and 4) are typically characterized by the need for hospitalization for symptom management. To date, few studies have quantified the magnitude of irAE's in hospitalized patients. Moreover, cancer physicians report being ill-prepared to manage patients with severe irAEs in the hospital.
Methods: This retrospective study evaluated patients with advanced malignancy treated with immune checkpoint inhibitors (until 12/13/2016) who experienced a suspected irAE that required admission to the Massachusetts General Hospital (MGH). Data was collected on hospitalized patients from 2011-2017 that received an immune checkpoint inhibitor: ipilimumab, pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, or a combination of these agents such as ipilimumab plus nivolumab,. In addition, oncologists at MGH were surveyed in 2016 regarding their confidence about managing patients with such irAEs.
Results: From 2011-2017, we identified a large number of hospitalizations for suspected toxicity related to immune checkpoint inhibitors (N = 422). The majority of these admissions (64.5%; N = 272) were confirmed toxicity, and patients were treated with immunosuppression or had therapy stopped as result of the irAE. Of this group, 68% were male, 31.9% were female and 9.6% (N = 26) had two or more toxicities diagnosed during the admission. The LOS on average was 5.99 days (ranging from 1 to 31 days), and readmission rate for another irAE event was 21.7%. The most common irAEs requiring hospitalization were colitis (34.9%), followed by endocrinopathies (18.2%), pneumonitis (10.2%), neurological complications (7.9%), hepatic complications (6.9%), dermatological complications (5.2%), rheumatological complications (3.9%), cardiovascular complications 2.3%), renal complications (2.3%), and heme complications (1.9%). Over the past 5 years, there was a significant increase in inpatient admissions due to irAEs (admissions in 2011 vs 2016, odds ratio = 3.67; p = <0.001). However, in the Cancer Center survey (N = 26), the majority (%) of MGH oncologists revealed that they do not feel very comfortable managing irAEs, and 48% even felt that complications from immunotherapy should be managed on a different service.
Conclusion: The number of patients admitted due to immune-related adverse effects (irAEs) has significantly increased at MGH since 2011. These irAEs may have catastrophic consequences resulting in prolonged hospitalizations and multiple readmissions, and in general, oncologists are not comfortable managing these side effects. The potentially devastating outcomes from irAEs requires that we prepare providers and patients for the wave of hospital admissions by developing a coordinated multidisciplinary approach and a translational research program for biomarker development to allow early detection and intervention.

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Pooyan Rohani, MD, MEngr, Dermatology

The Use of Optical Polarization Imaging to Aid Planning of Mohs Micrographic Surgery

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Introduction: Mohs micrographic surgery (MMS) is the treatment of choice for high risk non-melanoma skin cancers (NMSCs). However, often more than one surgical stage is required for complete clearance of a tumor, at times leading to more extensive and costly procedures. New technology is needed for more effective preoperative planning. **Objective:** To determine whether optical polarization imaging (OPI) can detect the extent of subclinical tumor spread.
Methods: A previously validated OPI tool was used to non-invasively and rapidly perform preoperative imaging of NMSCs on patients scheduled to undergo routine MMS. The surgeon was blinded from the preoperative imaging results. **Setting:** This pilot study was conducted in an outpatient surgical setting. Imaging was non-invasive and did not alter standard surgical planning. **Participants:** Patients over 18 years of age with biopsy-proven basal cell carcinomas participated. **Exposures**: The use of OPI preoperatively with wavelengths of 440nm and 640nm and power density of 0.38 mW/cm^2. **Main outcome and measure:** Whether preoperative assessment by OPI identifies tumor at the surgical margin of Mohs surgery specimens. **Results:** OPI technology accurately predicted the presence or absence of tumor at the surgical margin in 4 cases, as confirmed on histology.
Conclusion: OPI may provide a new avenue for more efficient preoperative MMS planning by identifying sub-clinical tumoral extension beyond visibly involved skin. Limitations exist and further studies are required.

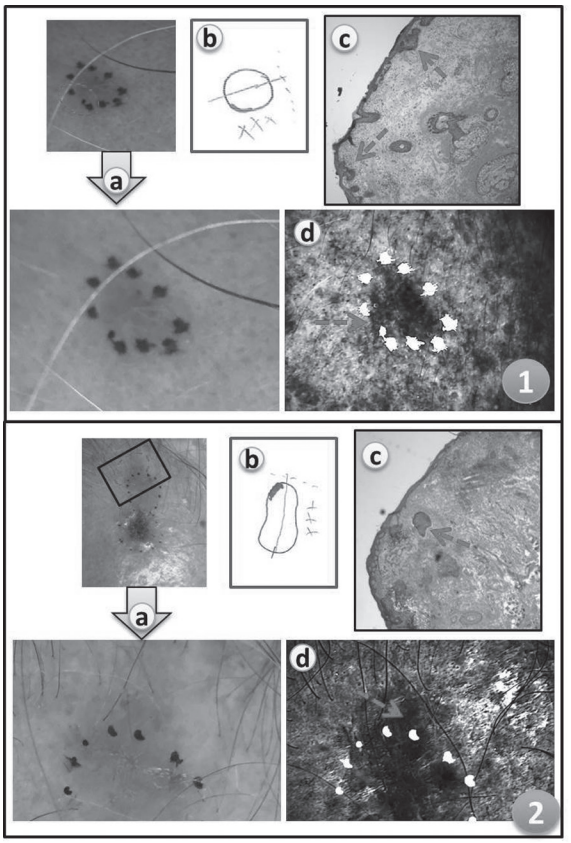

Figure 1) Cases 1 and 2 with tumor extension beyond the original surgical marking: a) Preoperative marking corresponding to the area to be excised. The larger clinical image is increased in size and rotated digitally to allow simpler comparison with the cross-polarized image. b) Intraoperative Mohs map. Red marks show tumor-involved margins. c) Intraoperative histopathological findings (high power), centered and rotated on positive surgical margins. Red arrows point to islands of basal cell carcinoma. d) Preoperative 440 nm cross-polarized image. The red arrow points to the tumor-involved area extending beyond the excision site.

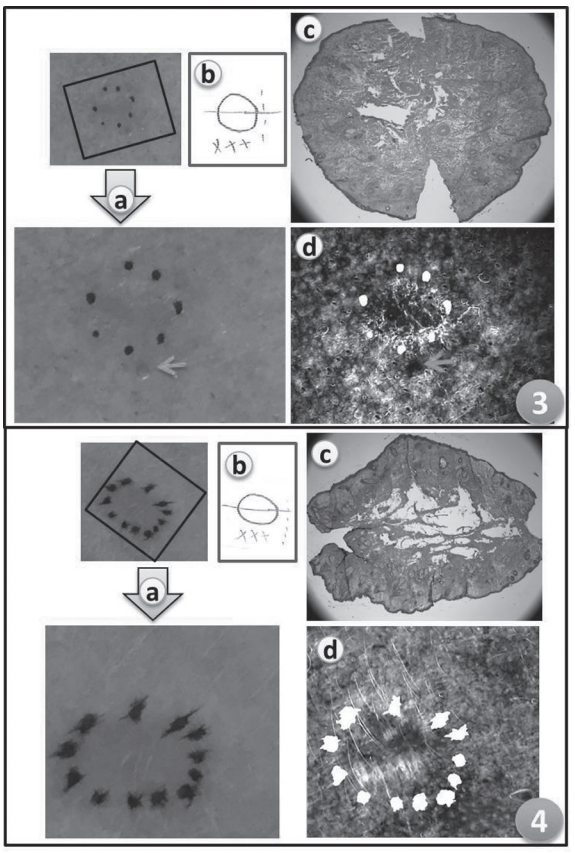

Figure 2) Cases 3 and 4 with tumor remaining within the original surgical marking: a) Preoperative marking corresponding to the area to be excised. The larger clinical image is increased in size and rotated digitally to allow simpler comparison with the cross-polarized image. b) Mohs map is recorded intraoperatively and blinded to imaging results. Margins were clear. c) Intraoperative histopathological findings (low power) showing uninvolved margins in the entire lesion. d) Preoperative 440 nm cross-polarized image. The green arrow highlights the shadow cast by a lentigo in polarized imaging.

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Adam Rokicki, Medicine - Cardiology

Observed vs. Predicted Cardiovascular Disease among Survivors of Cancer: A retrospective cohort study

A. Rokicki[1,2], D. Addison[1,2], A. Spahillari[2], A.W. Chan[3], L.J. Wirth[2], R. Shah[1,2] and T.G. Neilan[1,2]

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Introduction: Radiation-therapy (RT) is associated with an increase in atherosclerotic cardiovascular events (ASCVD: stroke, myocardial infarction and cardiovascular death). In broad populations, there are two sets of guidelines, ACC/AHA and USPSTF, which guide the use of statins. Both statin guidelines are similar in that they use the pooled cohort risk equation (PCE) to estimate the risk of ASCVD events but have different inclusion criteria. However, whether any of the two guidelines accurately predict ASCVD events among persons treated with RT is unknown.

Methods: From an institutional database, we identified all consecutive subjects treated with neck RT from 2002-2012 for head and neck cancer (HNCA). Patients with an established indication for statins or on statins were excluded. The primary outcome was an ASCVD event. The association between statin eligibility and events was determined using Cox proportional hazard models. Observed versus PCE-predicted ASCVD events were evaluated over increments of 1,000-patient years of follow-up and estimated C-statistics were used to exam concordance between predicted and observed post-RT events.

Results: From 1011 RT-treated HNCA subjects, 562 (55±12 years, 34% female, 29% HTN) were eligible for the ACC/AHA guidelines and 474 patients (57±8 years, 33% female, 31% HTN) were eligible for the USPSTF guidelines. Among those eligible for ACC/AHA guidelines, there were 65 observed ASCVD events over a median follow-up of 3.7 (1.7-6.4) years, and among those eligible for USPSTF guidelines there were 59 events over a median follow-up of 3.6 (1.7-6.3) years.

Statin eligibility using the ACC/AHA criteria was associated with an increase in observed post-RT events (HR: 1.9, CI 1.2-3.2, *P* = 0.01), but the ACC/AHA criteria for guiding statin use showed a low concordance with the observed events (observed ASCVD incidence 27.1 vs. 4.3 predicted per 1,000-person years; C-statistic 0.56; **Figure**). Statin eligibility using the USPSTF criteria displayed a trend toward an increase in the observed ASCVD events (HR: 1.8, CI 1.0-3.2, *P* = 0.06) but again had a low concordance with observed events (observed ASCVD incidence 26.3 vs. 4.6 predicted per 1,000-person years; C-statistic 0.53, **Figure**).

Conclusion: Among persons treated with RT, there is a markedly elevated risk of future CV events and both of the current standard primary prevention guidelines for statin therapy show poor performance in predicting future CV events among patients post RT. Future research includes either generating better risk-calculators among this vulnerable population or studies testing whether all patients post-RT should be treated with statins.

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Katherine Rosa, PhD, Nursing

Research and psychometric testing of a tool to measure nurse-patient relationship as healing transformation with persons living with chronic illness – Phase 1

K. Rosa

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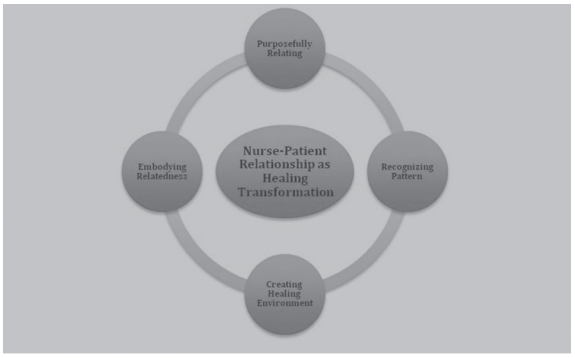
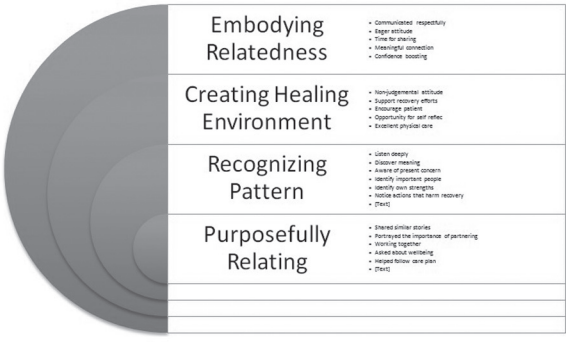
Introduction: Worldwide chronic diseases are at epidemic proportions and exceed infections as a threat to health. Problems related to chronic disease incidence, morbidity, and costs are predicted to rise over the next 30 years. The CDC reports that 86% of U.S. healthcare spending is allotted to treating chronic illness. Frequently, patients struggle to make needed lifestyle behavior changes. Recent evidence supports that when patients and their nurses are engaged in coming to know the patient's pattern of responses to meaningful people and events in life - then nursing care is patient centered, comprehensive, compassionate, and improves well being. While we know this style nurse-patient relationship fosters healing and wellbeing no scale measuring this phenomenon of relationship as healing transformations exists.

Methods: Phase 1 of instrument development followed the first four of eight procedural steps as outlined by DeVellis. Data were extracted from related literature and Rosa's recent integrative review on the use of the Newman praxis relationship in chronic illness. Initial codes were noted and grouped. Themes were defined and key variables identified using the clinical literature and lens of expert clinical practice on the healing transformative nature of nurse-patient relationship with persons with chronic illness. A pool of items was generated. Each item was assessed for readability, comprehension, and understanding by a team of nurse experts in relationship-based care.

Results: The nurse-patient relationship creates an environment for promoting opportunities and actions that promote patients' healing and personal transformation. Patients made new choices, found new meaning, and sustained behaviors fostering healing and well-being. Four themes emerged from the data - purposefully relating, recognizing pattern, embodying relatedness, and creating healing environment to describe the nurse-patient relationship as healing transformations. Based upon the four themes, 55 items were developed and submitted to six nurse experts in relationship-based care for content validity, readability, and understandability.

Conclusion: Items with 100% agreement by reviewers were used to develop a 6-point Likert- type scale to measure patients' perceptions of their nurse-patient relationship as promoting healing and wellbeing. Future work to complete psychometric testing of the Relationship as Healing Transformation scale is underway.





Relationship Environment Promoting Patients' Healing when Living with Chronic Illness

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Matthew Rosenbaum, M.D., Pathology

Immune Checkpoint Expression and the Tumor Immune Environment in Colorectal Carcinoma

M. Rosenbaum[1], J.R. Bledsoe[2], M. Kem[1], T. Huynh[1] and M. Mino-Kenudson[1]

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Introduction: Oncologic research into immunotherapy, particularly, immune checkpoint inhibition, is a burgeoning field with serious treatment considerations for patients. Programmed Cell Death Protein 1 (PD-1) axis blockade enhances anti-tumor immunity, leading to clinical response in microsatellite instability (MSI)-high colorectal cancers (CRC). Tumor cell PD-L1 expression is associated with treatment response in various tumor types but has shown heterogeneity, with some tumors responding poorly. Co-expression of additional actionable immune inhibitory targets, such as Indoleamine 2,3-Dioxygenase 1 (IDO1) may explain treatment failure in some of these immunogenic MSI-high CRCs. The biological role and clinical phenotype associated with tumor IDO1 expression has not been well studied in CRC.
Methods: A tissue microarray consisting of multiple cores from 171 cases of CRC was analyzed for PD-L1 and IDO1 immunohistochemical expression on tumor cells by using H-scores (graded as summed percentage of cells weighted by expression (0, 1+, 2+, or 3+) for a total of 0-300). We also examined CD8, TBET (a Th1 pathway activation marker), and GATA3 (a Th2 pathway activation marker)-positive tumor infiltrating lymphocytes (TILs). For each case, clinicopathologic data and follow-up was reviewed. The majority of tumors also had microsatellite instability and molecular analysis via the MGS SNaPshot next generation sequencing platform.
Results: : PD-L1 expression was seen in 19% of our CRC cohort, IDO1 in 24%. Both PD-L1 and IDO1 expression were associated with the serrated pathway of CRC carcinogenesis (older age, female sex, lower stage, high grade, medullary morphology, MSI-high status, BRAF mutation). PD-L1 and IDO1 were co-expressed in 12% of the cases, this phenotype was associated with the same MSI-H phenotype (older age, female gender, lower stage, higher grade, medullary morphology, CD8+/TBET+ TILs, MSI-high, BRAF mutations, and KRAS wild type). Isolated IDO1 expression (i.e. IDO1 positive, PD-L1 negative), was associated only with older age, lower stage, CD8+TILs, TBET+TILS, MSI-high status. In contrast, Isolated PD-L1 expression (i.e. PD-L1 positive, IDO1 negative), was associated only with TBET+ TILs and TP53 mutation.
Conclusion: IDO1 expression was found in approximately 1/4 of our CRC cohort, and was associated with features of serrated pathway CRC. This association was more significant in IDO1+/PD-L1+ tumors. Although PD-L1+ CRCs are known to exhibit a similar phenotype, PD-L1 expression in isolation was not significantly associated with these features, although a limited number of PD-L1 positive, IDO1 negative tumors may partially explain this lack of significance. Considering the frequent co-expression of PD-L1 and IDO1, IDO1 expression may be a confounding factor in many studies investigating the PD-1/PD-L1 axis blockade, particularly those targeting MSI-H cancers

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Matthew Rosenbaum, M.D., Pathology

Next Generation Sequencing Adds Value to Cytology and Fluorescence in Situ Hybridization in the Diagnosis of Bile Duct Brushing Specimens

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Introduction: Bile Duct Brushing (BDB) cytology is challenging with poor sensitivity for the detection of high-risk lesions (HRLs; e.g. high-grade dysplasia and malignancy). Fluorescence In Situ Hybridization (FISH) is reported to improve sensitivity and is standard of care for patients with primary sclerosing cholangitis with increased risk for malignancy. Here we present a large cohort of BDB samples analyzed with FISH and/or Next Generation Sequencing (NGS) to determine their comparative performance in detecting HRLs.
Methods: BDB cytology with FISH and/or NGS performed between 05/2014 and 04/2016 were reviewed with clinicopathologic followup. NGS was performed via the MGH SNaPshot multiplex PCR platform that sequences areas of 39 oncogenes. FISH was performed with the Urovysion probe set. Performance of cytology, FISH, and NGS were calculated based on clinicopathologic follow-up.
Results: 164 BDB specimens from 139 patients were reviewed. 137 patients had follow-up, either with follow-up resection/cytology, or clinical follow-up supporting a benign (62%) or malignant (38%) diagnosis. There were 20 positive, 14 suspicious, 39 atypical, and 92 negative for malignancy samples by cytology. Of the 147 with FISH, 32 were positive for chromosomal abnormalities (21.8%), and of the 156 with NGS, 44 had oncogenic mutations (28.2%), including *KRAS* (n=34), *TP53* (n=22), *SMAD4* (n=7), *GNAS* (n=5), *APC* (n=4), *FBXW7 (n=4), CDKN2A* (n=3), FOXL2 (n=3), *BRAF*, *PIK3CA*, and

FGFR2 (n=2 each), and *ERBB2*, *ESR1*, *STK11*, *CDH1*, *PIK3R1*, *MAP2K1*, *EGFR*, *DDR2* and *VHL* (n=1 each). The addition of FISH and NGS to cytology increased the percentage of positive cases with a malignant outcome from 50.8% to 86.7%. Sensitivity and specificity of cytology alone was 50.8% and 99%, increasing to 68% and 95% with FISH, to 78% and 96% with NGS, and improving to 87% and 92% with the combination of cytology, FISH, and NGS. Late mutations (defined as non-*KRAS/GNAS* pathologic mutations) had a 45% sensitivity and a 99% specificity for malignancy.
Conclusion: The addition of NGS resulted in improved sensitivity in the detection of HRLs compared to cytology or cytology with FISH. In addition, the use of granular data, such as non-KRAS/GNAS mutations may be used to increase specificity. On its own, NGS provides an improvement in sensitivity and specificity comparable to FISH. The routine use of NGS for BDB specimens adds significant value to cytology even with FISH. As assays and informatics pipelines improve, the additional value of NGS will likely increase as well. However, careful correlation with clinical and radiologic findings is critical as many pre-malignant neoplasms may harbor mutations.

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Julia Rosenbloom, Anesthesia, Critical Care and Pain Medicine

Race and Sex Both Affect Pain Management in the Emergency Department

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Introduction: Although racial and sex disparities exist in healthcare generally and pain management more specifically, the influence of both these sociodemographic factors together has not been well documented. The aim of this study was to examine the interaction of race and sex on administration of opioid analgesics in the emergency department (ED).
Methods: We conducted a retrospective review of the 2010-2014 CDC-NHAMCS data for patients aged 12-55 presenting to EDs with a primary diagnosis of appendicitis or gallbladder disease as defined by ICD-9 codes. We first performed univariate analysis to determine the frequency of opioid analgesia administration by sex within the racial groups of white non-Hispanic and non-white. Subsequently, multivariable analyses adjusted for pain score upon presentation, triage score, patient age, city/non-city location, day of the week, number of comorbidities, time of arrival to the ED, and US region to determine the association between sex and opioid receipt within white non-Hispanic and non-white groups.
Results: A weighted sample of 553 ED visits was included, representing 2,622,926 visits. The sample population was comprised of 392 (70.9%) females and 319 (57.7%) white non-Hispanics. In adjusted models, white non-Hispanic males are slightly less likely to receive opioids than white non-Hispanic females (OR=0.906, 95% CI: 0.899 to 0.913, $p<0.001$); non-white males are much less likely to receive opioids than non-white females (OR=0.508, 95% CI: 0.502 to 0.513, $p<0.001$) (Figure 1).
Conclusion: Based on NHAMCS data from 2010-2014, an interaction between race and sex exists for administration of opioid analgesia for all races, but is much more pronounced for nonwhites. These results suggest that disparities in opioid management may be predicated on the joint effect of patient race and gender, a condition that may be especially significant for non-white patients.

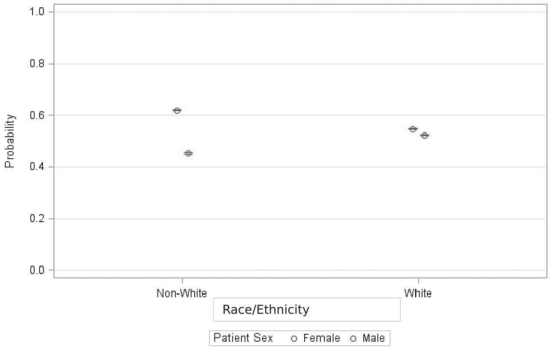

Figure 1: Adjusted probability (with 95% Confidence Intervals) of receiving opioids in the Emergency Department from 2010-2014 for white non-Hispanics and nonwhites, by sex. Female=blue; male=red.

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Trevor J. Royce, MD MS MPH, Radiation Oncology

Clinical characteristics and outcomes of non-urothelial cell carcinoma of the bladder: Results from the National Cancer Data Base

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Introduction: Limited data exist to inform the epidemiology and outcomes of non-urothelial cell bladder cancer (NUCBC) in the United States. This presents a challenge for clinicians and patients attempting to make informed treatment decisions when facing this diagnosis. We analyzed the presentation, treatment patterns, and outcomes of patients with NUCBC in the United States using the National Cancer Data Base.

Methods: 163,683 bladder cancer patients from 1998-2014 in the National Cancer Data Base were identified. 153,262 had urothelial cell (UC) carcinoma (93.6%) and 10,421 had NUBC (6.4%) further classified as: squamous cell carcinoma (SC, 2.4%), adenocarcinoma (AC, 1.7%), neuroendocrine (NE, 1.3%), micropapillary (MP, 0.3%), lymphoid/haematopoietic (LH, 0.3%), and sarcoma/mesenchymal (SM, 0.3%). Analyses were run on the entire cohort, those with nonmuscle invasive disease (T0-1, N0, M0), muscle-invasive disease (MIBC, T2-4A, N0, M0), and metastatic disease (T4B or N+ or M+). Clinical characteristics and treatment received (surgery, chemotherapy and radiation) were reported by histologic subtype. Survival analysis was performed via Kaplan-Meier estimates and Cox proportional hazards models.

Results: Patients with NE, SC, MP, and AC were more likely to be diagnosed with metastatic disease (11.5% for UC versus 40%, 31.3%, 17.8%, and 30.6%, respectively, $p < 0.001$) (Table). NUBC patients were also more likely to have MIBC compared to UC (43% versus 32.5%, respectively). Patients with UC were less likely to undergo cystectomy, chemotherapy, and radiation therapy ($p<0.001$). For all patients, NUBC, with the exception of LH, SM, and MP, was associated with inferior survival compared to UC ($p<0.001$) (Figure).

Conclusion: This encompassing clinical characterization and prognosis of non-urothelial cell bladder cancer patients in the US shows NUBC patients have significantly different disease characteristics compared to those with UC, and present with more advanced disease, receive more treatment, and overall have inferior outcomes. Further work is needed to help improve outcomes for these patients.

Variable	Total	UC	SC	AC	NE	MP	SM
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Group							
NMIBC	87573 (53.5)	85712 (55.9)	695 (17.7)	716 (25.7)	255 (12.2)	195 (34.7)	0 (0)
MIBC	54369 (33.2)	49884 (32.5)	2001 (51)	1214 (43.7)	1003 (47.8)	267 (47.5)	0 (0)
Metastatic	20683 (12.6)	17666 (11.5)	1227 (31.3)	851 (30.6)	839 (40)	100 (17.8)	0 (0)
Other (SM&LH)	1058 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	520 (100)
Age (Mean, STD)	70.8 (12)	71 (11.9)	70 (13.9)	64.9 (14.8)	69.9 (12.3)	69.2 (10.9)	65.5 (16.7)
Gender							
Male	120130 (73.4)	113958 (74.4)	1872 (47.7)	1785 (64.2)	1557 (74.2)	445 (79.2)	307 (59)
Female	43553 (26.6)	39304 (25.6)	2051 (52.3)	996 (35.8)	540 (25.8)	117 (20.8)	213 (41)
Tumor Grade							
Well Differentiated	9220 (5.6)	8671 (5.7)	323 (8.2)	172 (6.2)	10 (0.5)	8 (1.4)	30 (5.8)
Moderately Differentiated	22644 (13.8)	20501 (13.4)	1393 (35.5)	679 (24.4)	13 (0.6)	20 (3.6)	35 (6.7)
Poorly Differentiated	70772 (43.2)	67224 (43.9)	1331 (33.9)	1126 (40.5)	726 (34.6)	190 (33.8)	168 (32.3)
Undifferentiated	42157 (25.8)	40528 (26.4)	307 (7.8)	236 (8.5)	671 (32)	284 (50.5)	127 (24.4)
Unknown	18439 (11.3)	16338 (10.7)	569 (14.5)	568 (20.4)	677 (32.3)	60 (10.7)	160 (30.8)
Clinical T category							
1	89392 (54.6)	87345 (57)	752 (19.2)	761 (27.4)	330 (15.7)	202 (35.9)	2 (0.4)
2	50481 (30.8)	46503 (30.3)	1640 (41.8)	977 (35.1)	1096 (52.3)	260 (46.3)	5 (1)
3	8736 (5.3)	7584 (4.9)	542 (13.8)	343 (12.3)	218 (10.4)	48 (8.5)	1 (0.2)
4	9292 (5.7)	7818 (5.1)	750 (19.1)	448 (16.1)	242 (11.5)	31 (5.5)	3 (0.6)
Unknown	5782 (3.5)	4012 (2.6)	239 (6.1)	252 (9.1)	211 (10.1)	21 (3.7)	509 (97.9)
Clinical N category							
0	148154 (90.5)	140798 (91.9)	3090 (78.8)	2245 (80.7)	1529 (72.9)	480 (85.4)	12 (2.3)
1	4417 (2.7)	3821 (2.5)	253 (6.4)	140 (5)	176 (8.4)	27 (4.8)	0 (0)
2	4934 (3)	4316 (2.8)	264 (6.7)	135 (4.9)	180 (8.6)	39 (6.9)	0 (0)
3	1156 (0.7)	978 (0.6)	73 (1.9)	38 (1.4)	56 (2.7)	10 (1.8)	1 (0.2)
Unknown	5022 (3.1)	3349 (2.2)	243 (6.2)	223 (8)	156 (7.4)	6 (1.1)	507 (97.5)
Clinical M Stage							
0	149887 (91.6)	142326 (92.9)	3313 (84.5)	2224 (80)	1488 (71)	524 (93.2)	12 (2.3)
1	12565 (7.7)	10763 (7)	589 (15)	551 (19.8)	601 (28.7)	38 (6.8)	3 (0.6)
Unknown	1231 (0.8)	153 (0.1)	21 (0.5)	6 (0.2)	8 (0.4)	0 (0)	505 (97.1)
Surgery							
No Surgery	10579 (6.5)	8998 (5.9)	614 (15.7)	418 (15)	242 (11.5)	26 (4.6)	69 (13.3)
TURBT	121432 (74.2)	116147 (75.8)	1919 (48.9)	1266 (45.5)	1334 (63.6)	267 (47.5)	194 (37.3)
Partial Cystectomy	3192 (2)	2412 (1.6)	135 (3.4)	470 (16.9)	81 (3.9)	3 (0.5)	80 (15.4)
Complete Cystectomy	28480 (17.4)	25705 (16.8)	1255 (32)	627 (22.5)	440 (21)	266 (47.3)	177 (34)
Chemotherapy							
No	123081 (75.2)	116291 (75.9)	3042 (77.5)	1974 (71)	786 (37.5)	301 (53.6)	426 (81.9)
Yes	40602 (24.8)	36971 (24.1)	881 (22.5)	807 (29)	1311 (62.5)	261 (46.4)	94 (18.1)
Radiation Therapy							
No	147795 (90.3)	139392 (91)	3124 (79.6)	2386 (85.8)	1552 (74)	511 (90.9)	439 (84.4)
Yes	15888 (9.7)	13870 (9)	799 (20.4)	395 (14.2)	545 (26)	51 (9.1)	81 (15.6)

Table. Patient characteristics by histology, all patients.

Abbreviations: UC, urothelial cell carcinoma; SC, squamous cell carcinoma; AC, adenocarcinoma; NE, neuroendocrine carcinoma; MP, micropapillary; SM, sarcoma/mesenchymal; LH, lymphoid/haematopoietic; NMIBC, non-muscle invasive bladder cancer; MIBC, muscle-invasive bladder cancer; STD, standard deviation; RT, radiation therapy; CT, chemotherapy; TURBT, transurethral resection of bladder tumor.

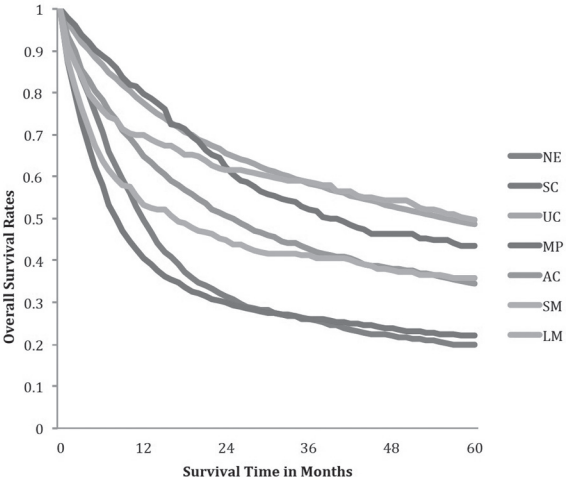

Figure. Kaplan-Meier survival curves by histology, all patients

Abbreviations: UC, urothelial cell carcinoma; SC, squamous cell carcinoma; AC, adenocarcinoma; NE, neuroendocrine carcinoma; MP, micropapillary; SM, sarcoma/mesenchymal; LM, lymphoid/haematopoietic

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Donna Rusinak, BA, Performance Analysis and Improvement/Practice Improvement

Improving the transition from acute to post-acute care: a collaborative model with TEAMHealth/IPC

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Introduction: The Joint Commission (2013) reports several activities that had positive effects on patient transitions between settings including: 1. Strong leadership support for new transition processes; 2. Positive relationships between the sending and receiving providers; 3. Handoffs that involve interpersonal communications (instead of only written or electronic communications); 4. Assigned accountability for transitions-related tasks. [1] In 2013, MGH faced inconsistent physician coverage which raised concern about the quality of care provided to MGH patients going to SNF. As a possible solution to this issue, MGH approached TeamHealth (formerly IPC Healthcare), a national physician group staffing hospitals and post-acute care facilities, to collaborate and provide clinical services to MGH patients in SNFs. Since that time, TEAMHealth has been actively involved in MGH's post-acute strategies to improve patient care in post-acute care facilities and has expanded to more SNFs in the MGH target regions. In 2015, as part of MGH's post acute strategy, MGH identified eleven local SNFs to be part of the MGH SNF Collaborative Network. The objectives include: sharing best practices and developing initiatives to improve care, reducing length of stay, and readmissions. The eleven SNFS were identified as having (1) a high volume, (2) a proven track record of collaborating, especially with challenging and vulnerable patients, and/or (3) clinical coverage by TEAMHealth, which practices in eight of the eleven MGH SNF Collaborative facilities. While the MGH has been working for years on reducing readmissions, in 2016 it was elevated further to a top priority. The Transition of Care (TOC) pilot was launched as part of the MGH Stay Connected Program, a bundle of programs designed to reduce readmissions at MGH. The TOC pilot ratchets up the connectedness between TeamHealth and the MGH [1] 2013 Joint Commission

Methods: Ouslander and colleagues highlight the critical importance of "warm handoffs" at the time of hospital discharge to SNF and the prevention of rapid transfers back to the ED. [2] The Transition of Care pilot (TOC) was designed to improve the handoff among acute hospitals, post-acute facilities, and primary care clinicians. TOC is the post-acute pilot in The Stay Connected Program, a bundle of readmission initiatives at the MGH. By embedding a TeamHealth Nurse Practitioner (NP) at the MGH, TOC is designed to create a seamless transition for a patient discharging to SNF. Following usual procedures, the MGH inpatient case manager processes the SNF referral using 4next, the electronic Partners' developed referral tool. Once the patient accepts the bed, a notification is sent via 4next to the TEAMHealth NP. Once notified, the NP reviews the chart with an eye on what would be important for a post-acute provider. The process includes a medication review with a specific focus on psychotropics, antibiotics, and pain medications. Additionally, the NP looks for the health care proxy (HCP), advanced directives, and MOLST form. If necessary the clinical team is consulted and also reminded to send the HCP and MOLST along with the patient The NP meets with the patient bedside and addresses any questions about the SNF and the upcoming transition. The NP then sends a detailed e-mail to the receiving TEAMHealth MD, the patient's primary care doctor (and specialists), as well as the iCMP care manager, if applicable. The NP is on-site at MGH Monday through Friday from 1pm – 4pm, peak SNF discharge hours, and has access to the pertinent clinical systems. [2] Ouslander J, Naharci I, Engstrom G, et al. Hospital Transfers of Skilled Nuring Facility (SNF) Patients Within 48 hours and 30 Days after SNF admission. JAMDA 17 (2016) 839-845.

Results: The pilot launched in November 2016; 350 patients have been seen with warm-handoff provided Too early to see any direct effect on readmission rates though baseline data indicate an opportunity to improve readmissions. Patients and providers across the continuum are very satisfied with the program and find the communication valuable. Clearly a great quality and safety initiative. SNFs note improvements in discharge summaries, prescriptions, and MOLST forms at the time of transfer While too early to show ROI, the program should also be seen as an a gateway to bundles and risk agreements. Funding and sustainability strategies (including the model from NP to Social Work or Nurse Case Manager) should be explored.

Conclusion: While it's too early to make data driven conclusions, this intervention appears to be moving us in the right direction to improve communication across the continuum. It is a low impact intervention that is yielding high satisfaction for patients, in patient providers, primary care and SNF providers. Provider communication outside the firewall is cumbersome, but a modifiable program barrier. Opportunities to intercept bounce backs in the ED, to be explored.

Sample email exchanges:

"…. She is nervous about rehab but knows it will help her build strength and get back on her feet. Of note, she is concerned about receiving her daily meds but reassured her a med list will be sent with d/c paperwork. She felt better after the discussion..."

"Dear XXX (PCP), Patient does not want to stay at the facility. PT did see him and cleared him for home with PT and services. Facility will make an appointment with your office for next week."

"Thanks. Would hold off on ASA, since she has had so many GI bleeds and several undiagnosed vaginal bleeds and very borderline HCT. Appreciate the coordination. Call or email any time."

"….. I am waiting on pathology on biopsy. Once I get this I will know what type of oncologist he needs and can arrange follow-up. He's hoping not to be at rehab for too long, mainly needs help with the macerated tissue in his perineum and wound."

"Thanks for taking care of her. I'd be happy to see her in follow up. Please let me know when she is closer to discharge so I can schedule her."

"I am currently away but am ccing my OP coverage Dr.XXX for his kind review. I am also ccing Dr. XXX, Ms. XXX's Cardiologist."

"Thanks for your detailed transition note. I am glad he's leaving the hospital but am curious if there was any discussion of him going home with hospice? In previous conversations with niece, she had spoken that he wanted to be home and she would support this. MOLST is clear for non invasive, DNR DNI, no vent, no hospital…."

"Dear XXX (PCP) Mr. XXX is a very fragile patient, and I have some concern about his long term plan and limited pulmonary reserve. Extremely congested …… Please don't hesitate to call me directly.

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Hatice D. Saatcioglu, PhD, Surgery - Pediatric

Exogenous MIS delays myometrium development in rats

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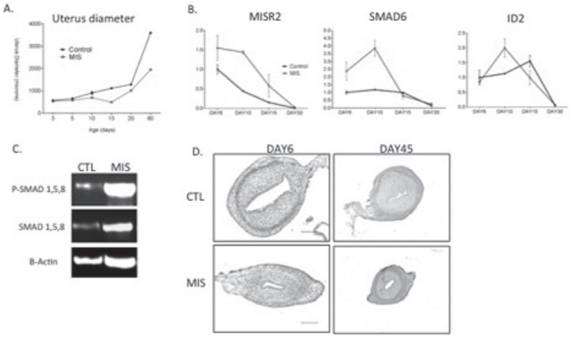
Introduction: During embryonic development, Mullerian inhibiting substance receptor-2 (MISR2) is expressed in the mesenchyme of the developing Mullerian duct, the anlage of the female reproductive tract (such as uterus, cervix, vagina, and fallopian tubes). As uterine development progresses, MISR2 expression becomes restricted to the myometrium layer, the smooth muscle layer of the uterus, which functions to induce uterine contractions. However, the role of MIS signaling during postnatal uterine development is not known. In male embryos, secretion of Mullerian inhibiting substance (MIS), the ligand of MISR2, by the embryonic testes causes regression of the Mullerian duct. As such, male mouse knockouts of MIS or MISR2 retain both a complete male and female reproductive tract, including uteri and oviducts. In females, MIS is produced by early granulosa cells of the ovary after birth, but its function on the uterus remains unknown. Understanding the role of MIS signaling during postnatal uterine development could help explain some disorders of myometrium patterning.

Methods: The adeno-associated virus serotype 9 (AAV9) gene therapy vector was used to deliver a more potent analog of MIS called LR-MIS. To test the role of MISR2 during uterine development, AAV9-MIS was were injected in newborn rats (on day 1), and the uteri of the rats were analyzed for diameter measurements, immunohistochemistry for a pan smooth muscle marker (Alpha-smooth muscle actin (α-SMA)), QPCRs (with primers designed for possible MISR2 signaling components), and western blots (for MISR2 signaling components) at different time points (from Day6, 10, 20, 30, and/or 45, n≥2, 1e11 particles/rat pup).

Results: The uterus size of the AAV9-MIS injected rats were smaller than controls, with a more pronounced difference on day 15 (A) (n≥2,p=0.0069). Known MIS signaling components such as MISR2, SMAD6, and ID2 were also up-regulated on day 15 in the treated uteri as shown by QPCRs (B) (n≥2). Preliminary western blot analysis also reveled that SMAD1,5,8, and phospho-SMAD1,5,8 were up-regulated in the MIS treated uteri (C). Further immunohistochemical analysis of smooth muscle actin in MIS treated and non-treated rat uteri showed that MIS-treated uteri have disorganized myometrium layer on Day 6, suggesting a novel function of MIS in regulating smooth muscle layer development in the uterus (n≥2, day 6 and day 10). We hypothesize that MIS regulates the developmental program of post-natal smooth muscle layer differentiation by antagonizing the TGF-beta canonical pathway through the upregulation of inhibitors (SMAD6 and ID2).

Conclusion: We showed that exogenous MIS retards uterine development by delaying the smooth muscle layer differentiation via an MISR2-SMAD6-ID2 pathway.



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Sassan Sabouri, MD, Anesthesia, Critical Care and Pain Medicine

Effectiveness of two regional anesthesia techniques, retrolaminar block and thoracic paravertebral block, on post percutaneous nephrolithotripsy pain control; a retrospective comparison with narcotic usage

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Introduction: Percutaneous nephrolithotripsy (PCNL) has become an attractive procedure for the treatment of large and complex kidney stones. PCNL involves the insertion of a large-bore, rigid scope into the renal pelvis to pulverize stones and remove subsequent fragments. This often results in severe post-operative pain, and increases the need for opioid analgesics. This is a retrospective study to compare the effectiveness of two different regional anesthesia (RA) approaches to the paravertebral space (PVS) for postoperative analgesia in PCNL: the retrolaminar block (RB) versus thoracic paravertebral block (TPVB). Postoperative pain control was also evaluated between the regional anesthesia (RA) group and the control group (No block: NB). Post operative pain in the NB group was controlled only with opioids.

Methods: After IRB approval, electronic and paper medical charts were reviewed from 290 adult patients undergoing PCNL at Massachusetts General Hospital from July 2014 to April 2016. A subgroup analysis of our study group was used to compare the effectiveness of two different approaches to the thoracic PVS, TPVB and RB. Primary outcomes include: Post anesthetic care unit (PACU) Visual Analogue Scale (VAS) for pain ("pain score"), percent of subjects using patient control analgesia (PCA), and total intraoperative and postoperative opioid use (in IV Morphine equivalents).

Results: There were no differences in demographics, including age, sex, weight and height, BMI, indication for PCNL and history of chronic pain, between RA and NB groups (Table 1). The RA group had a higher ASA status (P= 0.01). Also notable, was a higher reported history of ethanol use in the RA group (p= 0.06). Opioid consumption was not significant between the two groups on the first postoperative day one (PO#1)(P= 0.159); however, there was significantly higher need for PCA utility in the NB group (p=0.01), which was not accounted for in the total opioid amount due to inconsistent reporting of drug usage. Subjects who received either regional technique had a significantly lower incidence of post-operative nausea and vomiting (11% versus 33%, p = 0.02), lower PACU maximum pain score (2.5 versus 4.7, p = 0.003) and a trend towards lower intraoperative morphine use (5.1 mg versus 7.6 mg, p = 0.06) compared to the NB group. The regional anesthesia group was reported by nursing observation to have more alertness while in the PACU (18.5%, p <0.001) compared to the NB group. Analysis between the two regional approaches did not yield any significant difference in total intraoperative or PACU opioid requirement. Additional parameters which may be indirectly attributed to pain control – namely, PACU length of stay, time to first pain medication, time to first oral intake, PACU analgesics – were also not significantly different between the TPVB and RB arms(Table 2).

Conclusion: Our study showed that patients who undergo PCNL with regional anesthesia have better pain control in PACU but similar narcotic usage in POD#1 compared with patients who do not receive regional anesthesia. Subgroup analysis of patients with regional anesthesia with either RB and TPVB approaches, seem to have similar efficacy in regards to postoperative pain control and opioid usage.

Table 1- Demographics

Variable	NB (N=1250	RA(N=1250	P-value
AGE (mean (sd))	56.46 (13.14)	57.97 (15.14	0.385
Sex = Male (%)	75 (60.5)	74 (49.3)	0.085
Weight_kg (mean (sd))	82.22 (25.54)	85.30 (21.77)	0.289
Height_in (mean (sd))	66.36 (4.28)	66.55 (4.07)	0.721
BMI (mean (sd))	28.76 (8.49)	28.76 (8.49)	0.24

Table 2- Pain related varaibles in two different approaches to PVS

Variable	Thoracic paravertebral block	Retrolaminar block	P-Value
PACU LOS-min (median [IQR])	467.00 [366.00, 628.00]	403.00 [374.00, 538.00	0.465
Time to first pain meds-min (median [IQR])	45.00 [20.00, 75.00	45.00 [15.00, 90.00]	0.82
Total Equal IV Morphine-mg (median [IQR])	14.00 [10.00, 19.75]	13.33 [11.33, 17.50]	0.856
PACU Analgesics = Y (%)	31 (30.7)	3 (33.3)	0.999
Phenylephrine- mcg (median [IQR])	596.00 [150.00, 2305.00]	120.00 [43.75, 320.00]	0.051

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Sassan Sabouri, MD, Anesthesia, Critical Care and Pain Medicine

Spread of injectate solution during T4 Retromainar Block (RB); a study on eight fresh frozen cadaveric models

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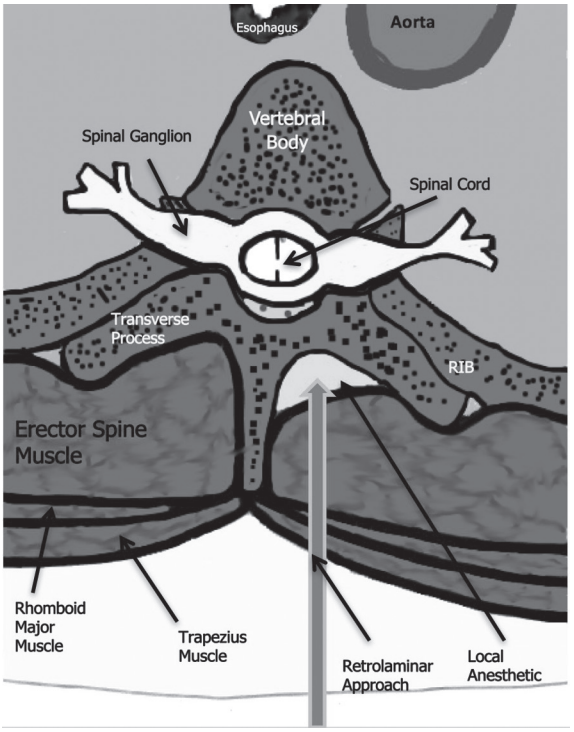
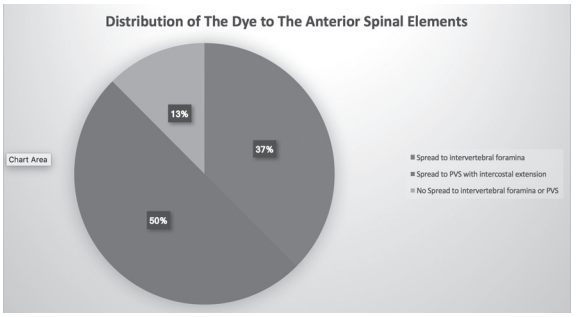
Introduction: The retrolaminar approach to thoracic paravertebral space (PVS) has been described to provide analgesia to the trunk and abdomen in a variety of clinical settings including breast and thoracic surgery and rib fractures. This approach involves injection of LA into the plane between lamina and paraspinous muscles (Figure1). Analgesia in RB is postulated to occur by blockade of thoracic spinal nerves, however the pattern of LA spread and the mechanism of spinal nerve blockade with this technique is unknown. We undertook a cadaver study to determine the pattern of injectate spread in RB. Specifically, we set out to describe the extent of spread within the retrolaminar plane as well as the extent of spread, if any, to the paravertebral, epidural, and intercostal spaces

Methods: This study has been exempted from Partners' Board of Ethics (IRB protocol #2015P002632). In each cadaver and in prone position, the spinous process of T4 is identified by surface and ultrasound. The 7-12 MHz ultrasound linear probe is placed approximately 1.5 cm lateral to this point in the sagittal plane, and lamina is visualized. Under ultrasound visualization, a 22 G, 80 mm block needle was inserted and advanced to contact lamina with in-plan approach. 20 ccs of mixture of Methylene Blue and Bupivacaine 0.5% was injected. Two cadavers had injections at the level of T9 and another had Thoracic Paravertebral Space (TPVB) at T4 in adition to T4 RB. Following the injection, midline dissection was performed down to the paraspinal muscles. The muscles were examined for signs of dye spread, then the epidural space was exposed. The cadaver was then flipped supine and attention turned to the anterior spinal elements. The parietal pleura was removed at the T4 level and the foramen exposed at this level to examine for dye spread.

Results: There were 5 female and 3 male cadavers with average age of 78 Y/O (range 70-102) with average BMI of 28.9. All the RB injections were done at the level T4(2 injections on the right and 6 on the left). Median depth of T4 lamina was 2.5 cm (Range 2.2-3.5 cm). Spread of dye under the skin happened in 1 of the cadavers. Spread of dye over the retrolaminar grove and under the paraspinal muscles was notified in all of the cadavers. Median cephalad spread of dye at T4 was 3.5 cm (range of 2-6 cm). Median caudad spread of dye at T4 was 10.7 cm (range of 9-20 cm). Median maximum lateral spread under the paraspinal muscles was 2.5 cm (range of 2.5-5 cm). Extension of the dye to the other side of spinous processes happened in 70% of cases (5 cadavers). In evaluation of the anterior spinal elements, obvious spread of the dye under the pleural was seen in 3 out of 8 cadavers. After removal of the pleura and endothoracic fascia, dye was notified in paravertebral space (PVS) in 4 cadavers, intervertebral foramina in 3 cadavers and no extension in one (figure 2). Maximum extension of the intercostal spread ranges between 1-5 cm and all the level of T4. Extension of dye into the thoracic intervertebral space was limited to 2-4 interspaces (median of 2) and in 6 out of 7 of them were betweenT3-T5. T4 RB and T9 RB showed similar pattern. TPVB showed spread from T1-T6 in the paravertebral space with maximum 15 cm of lateral spread.

Conclusion: This is the first cadaveric study of evaluation and study of spread of local anesthetic injection in the thoracic retrolaminar block. This showed that local anesthetic mixed with dye was found at either level of intervertebral foramina or PVS in 7 out of 8 cadavers. However, compare to TPVB spread is limited to 2 intercostal spaces. Spread is not predictable whether it goes to PVS of intervertebral foramina. One reason could be the difference in tissue resistance between cadavers. This study is compatible with prior clinical studies showed that RB is effective in postoperative pain control in selected cases. Meanwhile based on this study RB should be done, closely, at the level which cover the incision as the spread is limited. This study did not show the path of spread, since imaging modalities were not done on the cadavers. Effect of injection pressure during performing RB and time of spread was not evaluated in this study. Tissue resistance is different between cadavers and living human and more study in human can show more precise distribution of local anesthetic after RB.





Schematic view of thoracic paravertebral space and retrolaminar block

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Caitlin R. Sacha, MD, OB/GYN

The impact of male factor infertility on early and late morphokinetic parameters: a retrospective analysis of 4131 time-lapse (TL) monitored embryos

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Introduction: The optimal values of certain morphokinetic parameters correlate with an embryo's ploidy status and potential for blastocyst development and implantation. TL-morphokinetics might be affected not only by inherent embryonic traits but by both external factors (laboratory, culture) and patient-related characteristics. Evidence of paternal influence on embryonic genome activation, early embryonic development, and blastocyst formation in-vitro has been reported. The potential impact of paternal factors and male infertility diagnosis, if any, on early and late morphokinetic parameters, remains unclear. The aim of this study was to determine the effect, if any, of male factor infertility (MFI) on early- and/or late-morphokinetic parameters obtained during embryonic culture to blastocyst stage in a TL-monitored incubator.
Methods: This was a retrospective cohort study performed at a large academic fertility center. Data were collected from 4131 embryos derived from 602 IVF cycles (536 women) cultured to the blastocyst stage in a TL-monitored incubator (9/2013-9/2016). MFI embryos were compared to those derived from patients with other diagnoses (OTHDx), in regards to the following early- and late-morphokinetic parameters, defined as time period in hours from: i) tPNf to 1st cytokinesis (P1), ii) 2- to 3-cells (P2), iii) 3- to 4-cells (P3), iv) 4- to 5-cells (P4), v) 5-cells to early blastulation (P5SB), vi) pronuclei fading to early blastulation (PSB). Generalized fixed and random effects models, t-test, chi-square were used as appropriate. $P<0.05$ was considered statistically significant.
Results: Patients with MFI were younger, with higher antral follicle counts (AFC) and AMH levels than the OTHDx ones. As expected, ICSI was utilized more frequently among MFI patients than among those with OTHDx (91% vs. 36%, $P<0.001$; respectively). MFI patients produced fewer usable embryos (selected for either transfer or cryopreservation) than those with OTHDx (43% vs. 47%, $p=0.009$, respectively). MFI embryos when compared to OTHDx ones (unadjusted models) divided faster at most of the early cleavage stages (P1: 2.77 (1.25) vs. 2.85 (1.43) hrs, $p=0.039$; P2: 9.35 (4.65) vs. 9.71 (4.42) hrs, $p=0.026$; P4: 9.26 (6.21) vs. 10.01 (6.32) hrs, $p<0.001$) and slower at the later stages of embryonic development (PSB: 75.59 (8.96) vs. 74.49 (9.18) hrs, $p=0.005$; P5SB: 51.67 (10.96) vs. 49.72 (10.94) hrs, $p<0.001$). When multilevel generalized

linear mixed-effects models were fit, adjusting for potential confounders, P1-P4 did not differ significantly between the groups. These results did not change when embryos from patients with OTHDx were compared to those with either mild or severe MFI, or when usable embryos were analyzed separately from discarded ones (Table 1). However, when analysis was restricted to ICSI embryos only, embryos from severe MFI patients divided slower than mild in P2 by 0.83 hrs (95%CI: 0.02, 1.65; p=0.045), and mild MFI embryos divided faster than OTHDx ones in P2 by 0.98 hrs (95%CI: 0.18, 2.07; p=0.013). Moreover, when adjusting for all confounders but fertilization method, mild MFI embryos divided slower than OTHDx ones in regards to both P5SB and PSB periods by 1.67 hrs (95%CI: 0.08, 3.27; p=0.040) and 2.71 hrs (95%CI: 0.50, 4.92; p=0.016), respectively.

Conclusion: Overall, couples with MFI diagnosis produced a lower percentage of usable embryos than those with other diagnoses. In unadjusted models, MFI compared to OTHDx embryos appeared to divide i) faster at the early cleavage stages and ii) slower at the later-stages of embryonic development. After adjusting for potential confounders and either restricting analysis to ICSI-only embryos or ignoring fertilization method, most observed differences lost their significance and few persisted only for periods P2, P5SB, and PSB, a result suggesting a possible effect of fertilization method on certain morphokinetic parameters.

Baseline demographic and cycle characteristics of the study population

	MFI (N = 227)	OTHDx (N = 309)	
	Median (IQR)	Median (IQR)	P-value
Age, years	34.8 (32.5, 38.0)	35.9 (32.9, 39.0)	0.042
BMI, kg/m^2	23.5 (21.3, 28.2)	23.0 (21.3, 26.3)	0.160
Basal FSH, IU/L	6.7 (5.7, 8.0)	7.0 (5.7, 8.3)	0.300
AFC	15.0 (12.0, 20.0)	14.0 (10.0, 19.0)	0.030
AMH, ng/ml	3.2 (1.6, 5.5)	2.3 (1.2, 4.2)	0.003
Fertilization Method (%)			<0.001
ICSI	207 (91.2%)	110 (35.6%)	
Conventional Insemination	20 (8.8%)	199 (64.4%)	

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Roberta Santiago, MD, PhD, Anesthesia, Critical Care and Pain Medicine

Titration of positive end expiratory pressure restores homogeneous ventilation in mechanically ventilated hypoxic obese patients.

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Introduction: Obese patients when mechanically ventilated often develop hypoxic respiratory failure requiring prolonged ventilation. In prior studies in intubated critically ill obese patients (*Pirrone et al in CCM 2016 and Fumagalli et al in CCM 2017*), we found that selecting elevated positive end-expiratory pressure (PEEP) levels are required to improve lung compliance and restore oxygenation. PEEP is the pressure generated by the ventilator, at the end of each respiratory cycle, to mantain lung volumes at functional residual capacity in anesthetized mechanically ventilated patients. However, in obese patients, the effect of high levels of PEEP on ventilation distribution is not yet well described. We hypothesized that setting a titrated PEEP level after recruiting the lung will homogenize ventilation distribution and avoid collapse.

Methods: Respiratory mechanics were studied by recording airways pressure and flow waveforms. Lung morphology represented as percentage of collapse, overdistension and regional ventilation distribution (dependent / non-dependent percentage) was studied by electrical impedance tomography (EIT), a bedside non-invasive radiation-free imaging technique. A stepwise decrease in PEEP (Decremental PEEP trial) was performed after a recruitment maneuver in order to identify the level of PEEP (Titrated PEEP) resulting in the best compliance of the respiratory system. The study design included two PEEP steps: 1) PEEP=12 cmH_2O, value commonly set in obese patients by the intensive care unit team at our institution (ICU-PEEP); 2) PEEP according to a Decremental PEEP trial (Titrated-PEEP). At the end of each step arterial blood gas samples were collected. (Figure 1)

Results: Nine obese mechanically ventilated patients were enrolled (BMI 57±4.5). At ICU-PEEP, 27.5±5.5% of lung was collapsed and ventilation of the dependent lung region was reduced to 35±2.7%. Titrated-PEEP reversed lung collapse (estimated lung collapse 3.5±0.9%, $p<0.05$ *versus* ICU-PEEP) and balanced distribution of ventilation between the dependent and non-dependent lung region (dependent lung region: 51.6±3.8% $p<0.05$ *versus* ICU-PEEP). As a result of decreased lung collapse and improved regional ventilation, oxygenation and respiratory mechanics improved at Titrated-PEEP (PaO_2 increased from 137.8±33.1 mmHg to 315.6±31.7 mmHg, $p<0.05$ ICU-PEEP *versus* Titrated-PEEP; compliance improved from 35.3±4.0 ml/cmH_2O to 48.4±5.6 ml/cmH_2O, $p<0.05$ ICU-PEEP *versus* Titrated-PEEP). (Figure 2)

Conclusion: A decremental PEEP trial after a recruitment maneuver improves oxygenation and restores lung mechanics by homogenizing ventilation distribution and reducing the amount of lung collapse.

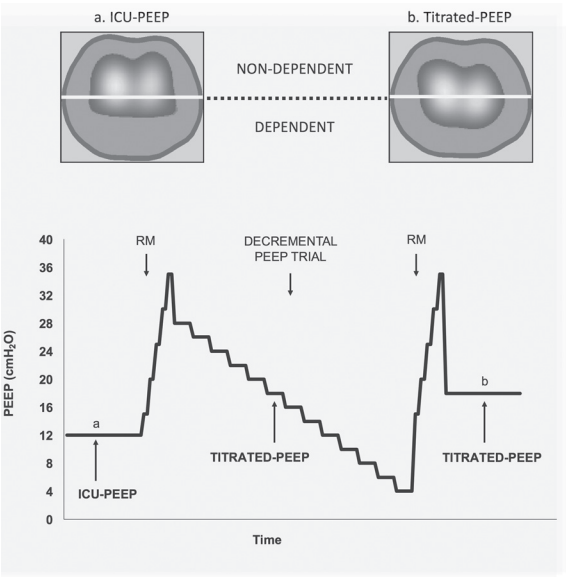

Figure 1. In a) and b) Two lung EIT images. a) ICU-PEEP. Ventilation appears to be predominated in the non-depedent regions of the lungs. b) Titrated-PEEP. Ventilation appears to be equally distributed in the dependent and non-depedent regions of the lungs.

Under a) and b), a schema regarding the levels of PEEP during the Study Protocol. ICU-PEEP, 12 cmH_2O, is the baseline PEEP. After a recruitment maneuver (RM) a Decremental PEEP trial was performed and Titrated-PEEP was identified. After a second RM, Titrated-PEEP was set. In this figure Titrated-PEEP is arbitrary selected as an example.

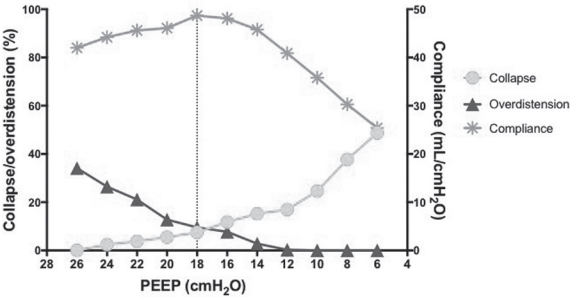

Figure 2. Decremental PEEP trial evaluated by EIT of one patient. The bell shape of the compliance of the respiratory system curve during a Decremental PEEP trial is the result of the balance between lung collapse and overdistension. Titrated-PEEP is selected as the level corresponding to the highest value of compliance during the Decremental PEEP trial, matching the lowest level of collapse and overdistension.

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Alveolar Type II Cells are Regulated by SLIT3 in Postnatal Lung Culture

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Introduction: Respiratory failure from lung hypoplasia is the leading cause of death in patients with congenital diaphragmatic hernia (CDH). We aim to identify the mechanism of defective pulmonary development in CDH, which would allow us to address the respiratory deficit that persists in these patients despite surgical repair. Based on phenotypic analyses and gene expression studies in animal models, and whole exome sequencing analysis of a large human cohort, we hypothesize that SLIT3 and its receptors play an important role in alveolarization during lung development, and that their pathogenic variants could contribute to CDH.
Methods: Lungs from four-day-old C57BL/6J mouse pups were inflated and cultured for four days *ex vivo* in media containing polyclonal goat IgG SLIT3 neutralizing antibody (AF3629-SP, R&D Systems). Light microscopy and immunofluorescence images were digitally captured for morphometric and quantitative analyses (Keyence BZ-X710 microscope). SYBR Green qPCR was performed to measure mRNA levels in organ culture and cell-based assays. Statistical analysis was done using paired t-test between treated and untreated samples from the same donor animal (significance level $p<0.05$).
Results: We observed that SLIT3 and its receptor, ROBO1, have peak expression in mouse lungs after birth, during alveolarization (Fig. 1A), and are co-expressed by the alveolar type II cells (ATII cells) (Fig. 1B, C). On histology, lung explants treated with the SLIT3-neutralizing antibody were found to have focal thickening of the interstitium (Fig. 1D vs E). A significant increase in the number of prosurfactant protein C-positive (pSPC+) ATII cells (Fig. 1H, $p<0.05$) was observed by immunofluorescence (Fig. 1F vs G) and confirmed by *Sftpc* qPCR (Fig. 1I). In addition, qPCRs for matrix metalloproteinases, *Mmp2* and *Mmp9* (not shown), which are downstream effectors in the SLIT/ROBO pathway, revealed a significantly increased expression ($p<0.05$) in the treated explants, suggesting remodeling of the extracellular matrix.
Conclusion: We propose a role for SLIT3 in the autocrine regulation of proliferation and/or differentiation of ATII cells during postnatal alveologenesis in the mouse lung. ATII cells are responsible for surfactant production and are thought to transdifferentiate into alveolar type I cells. Furthermore, an increase in ATII cells with concomitant surfactant deficiency has been reported in the lungs of CDH patients. While our observations suggest matrix-mediated remodeling of the alveolar

epithelium, further studies are needed to ascertain the exact mechanism behind the increase in ATII cells in order to uncover potential therapeutic targets.

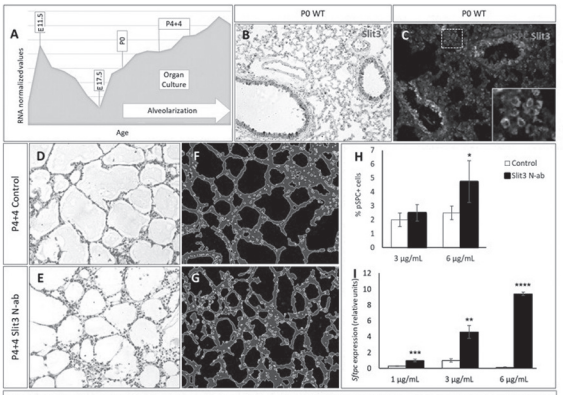

Figure 1 **A** The increased postnatal expression of *Slit3* coincides with bulk alveolarization in mice, spanning from P4 to P14. **B** SLIT3 is expressed in the proximal airway epithelium and by scattered cells in the interstitium of a normal murine lung at P0. **C** The interstitial expression of SLIT3 is localized to ATII cells, as evident from co-staining with pSPC. **D, E** H&E microscopy of the lungs shows thicker interstitium in explants treated with the SLIT3 N-Ab, compared to the controls. **F, G** Cell counts normalized by calculating the pSPC+ area (red) as a percentage of the total pulmonary interstitial area (blue). **H** Percentage of pSPC+ cells is higher in the SLIT3 N-Ab-treated samples, and a greater increase is seen with a dose of 6 µg/mL ($p<0.05$). **I** *Sftpc* expression increases significantly in the cultured lung explants with higher concentrations of Slit3 N-Ab.

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Nicholas Sauder, BA, Orthopedics

Risk Factors for Acetabular Component Malpositioning in Metal-on-Metal Hip Arthroplasty

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Introduction: Metal-on-metal (MoM) total hip arthroplasty (THA) and hip resurfacing arthroplasty (HRA) were widely used in the early 2000's before high revision rates and recalls prompted their use to sharply decline. Many MoM failures have been attributed to adverse local tissue reactions secondary to implant wear. Implant wear, in turn, has been linked to acetabular component malpositioning by mechanism of edge-loading, wherein the contact patch on the femoral head extends beyond the cup rim of the acetabular component. In addition to increasing wear risk, malpositioning is also linked to increased rates of dislocation and impingement. Therefore, proper intraoperative acetabular component placement in MoM THA and HRA is essential in minimizing the risk of postoperative complications and extending the longevity of the prosthesis. Component positioning is affected by patient, implant, and surgical technique factors. The current literature investigating these factors has been inconsistent. Although the use of MoM devices has diminished, it is important to understand the factors that contributed to MoM failure in order to avoid problems in future implant designs. The primary objective of this study was to characterize the acetabular component positioning of patients treated with one type of MoM hip system from an international, prospective study. The secondary objective was to determine independent predictors of acetabular component malpositioning.
Methods: Patients were selected from an international, prospective, multi-center study of the Articular Surface Replacement (DePuy, Warsaw, IN, USA). Subjects were enrolled at a mean time of 7.6 (range 3.4–11.4) years from primary THA. Patients with complete surgical and patient data reported were included in the present analyses. In addition, all patients had an anteroposterior and shoot-through lateral radiograph. This yielded the inclusion of 771 hips from 739 patients. Demographic information for the final patient cohort is listed in Table 1. The radiographs were assessed for acetabular inclination and anteversion using the mDesk software (RSA Biomedical, Umeå, Sweden). The acetabular positioning target zones were defined using values established in previous literature of 35° to 50° for inclination and 5° to 25° for anteversion. Patient, implant, and surgical variables were tested for association with component positioning in each target zone separately and in a combined target zone considering both inclination and anteversion. Univariate tests and binary logistic regressions were used.
Results: Acetabular component positioning varied greatly in our cohort (Figure 1). While most patients (66.0%) were found to be within the inclination target zone, a majority (61.1%) were placed outside of the anteversion target zone. As a result, only 24.1% of patients were in the combined target zone (Table 1). In both univariate and binary logistic regression analyses, the following variables were associated with an increased risk of acetabular component malpositioning outside of the combined target zone: anterior surgical approach ($p=0.002$; Odds Ratio (OR) = 0.44), large femoral head size ($p=0.001$; OR=0.53), female sex ($p<0.001$; OR=0.47), and THA arthroplasty type ($p=0.008$; OR=0.59). Age ($p=0.069$), dysplasia ($p=0.183$), and obesity ($p=0.786$) did not have a significant effect on component placement within the combined target zone.
Conclusion: It was alarming that only 24.1% of the whole cohort was in the acetabular inclination-anteversion target zone. This was largely due to the fact that a majority (56.4%) of the patients were over-anteverted (>25°). We found that female sex,

large femoral head size, THA arthroplasty type, and the direct anterior surgical approach were all independent risk factors for acetabular component malpositioning. These results showed differences to the current literature and may have been due to unique design and instrumentation features of the ASR implant system. This would suggest that future studies of component malpositioning risk factors and consequences should endeavor to analyze single implant types to better control for design features and assess the validity of a 'safe zone.'

Table 1. Summary patient and surgical demographics.

Variable	Value
Number of patients	771
Female sex (vs male)*	273 (35.4)
Dysplastic (vs primary osteoarthritis)*	43 (5.6)
Age†	63.5 (27.3 – 90.4)
BMI†	28.4 (17.6 – 51.9)
Obese (vs BMI < 30)*	255 (33.1)
Anterior approach (vs other approaches)*	223 (28.9)
MoM THA (vs MoM HRA)*	369 (47.9)
Large Femoral Head (vs small)*	414 (62.5)
Acetabular Inclination°†	43.5 (20.5 – 69.5)
Within Inclination Target Zone*	509 (66.0)
Acetabular Anteversion°†	26.1 (0.2 – 66.7)
Within Anteversion Target Zone*	300 (38.9)
Within Inclination and Anteversion Target Zone*	186 (24.1)

* Values given as N (%). † Values given as mean (range).

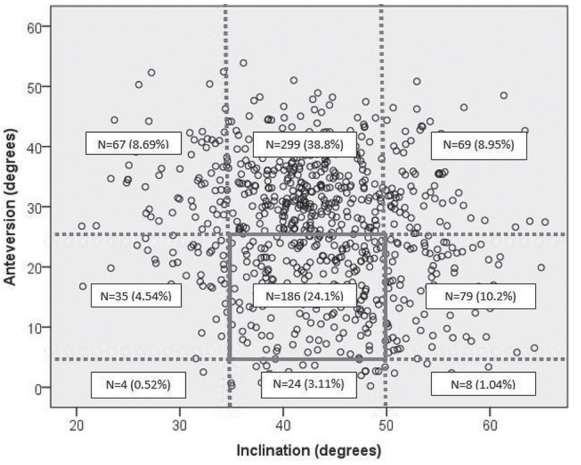

Figure 1. Scatterplot of inclination and anteversion angles for all acetabular components. The rectangular window represents the target zone range.

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Jessica Schleifer, MD, Emergency

The added value of ultrasound for the NEXUS Chest decision instrument in blunt trauma patients

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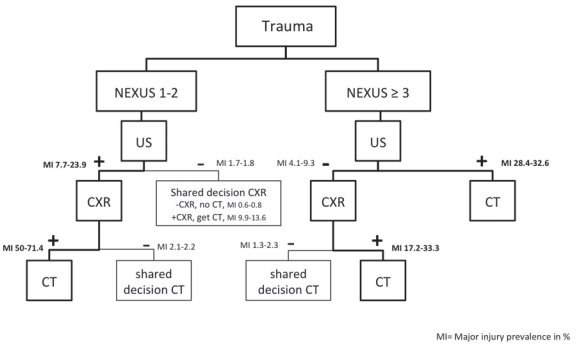
Introduction: Chest Radiographs (CXR) and chest computed tomography (CT) are frequently implemented in the care of patients with blunt trauma. The National Emergency X-ray Utilization Study (NEXUS) developed a decision instrument (DI) to identify a very-low risk population of patients with blunt trauma in whom imaging could be avoided. The 7 NEXUS criteria used are: age > 60, rapid deceleration mechanism (fall from high > 20 ft or MVC >40mph), chest pain, intoxication, altered mental status, distracting painful injury, tenderness to chest wall palpation. Ultrasound (US) in trauma patients is widely used, but not yet incorporated in the NEXUS DIs. In this study we sought to evaluate the added value of ultrasound in patients with blunt trauma.

Methods: This was a secondary analysis of prospectively collected cohorts of patients with blunt trauma at 9 Level 1 trauma centers in the United States that were enrolled in NEXUS chest studies between December 2009 and January 2012. The value of thoracic US was evaluated for different NEXUS scores and correlated with the prevalence of having a major injury (MI). Patients had US assessing for abdominal/thoracic free fluid, pneumothorax, and pericardial fluid. Not all patients were assessed for all findings.

Results: 6087 of 11477 patients had any US. 3298 of these patients had all three US. Table 1 summarizes the rates of MI, stratified by NEXUS score and result of CXR. Based on these results, we developed an US-based algorithm (Figure 1) for evaluation of trauma patients, showing rates of MI in each arm.

Conclusion: The rates of MI in trauma patients increase as the NEXUS Chest score increases. Rates of MI decrease when all US were negative. Ultrasound can be used in combination with CXR and NEXUS Chest score in risk-stratifying patients for major injury and can inform decisions about further imaging. Additionally, this adds new information about how to incorporate ultrasound findings into clinical decision-making and should be included in ultrasound education.

Major injury	NEXUS = 0 (5/848)		NEXUS = 1 (31/1858)		NEXUS = 2 (55/1743)		NEXUS = 3 (68/1084)		NEXUS > 3 (64/554)	
	CXR - (0)	CXR+ (5)	CXR - (9)	CXR+ (22)	CXR - (11)	CXR+ (42)	CXR - (16)	CXR+ (49)	CXR - (15)	CXR + (47)
all 3 US-	0.0%	8.7%	0.6%	13.6%	0.8%	9.9%	1.3%	17.2%	2.3%	33.3%
US+	0.0%	33.3%	2.2%	50.0%	2.1%	71.4%	3.9%	64.7%	18.2%	47.8%



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Melanie Schorr, Medicine - Endocrine-Neuroendocrine

Sarcopenic Obesity is a Risk Factor for Metabolic Syndrome in Young Adult Men, but not Women

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Introduction: Sarcopenic obesity, reduced skeletal muscle mass in the setting of obesity, is an important cardiometabolic risk factor in the elderly. Skeletal muscle mass is generally greater in young adults with overweight/obesity compared to lean controls, in part due to higher mechanical load (weight). However, relatively lower skeletal muscle mass may be an underappreciated mechanism linking overweight/obesity to cardiometabolic risk in young adults, and may have the potential to identify those at higher cardiometabolic risk in order to offer targeted prevention and treatment strategies to reduce long-term morbidity and mortality. We hypothesized that relative sarocopenia is associated with metabolic syndrome (MetS), type 2 diabetes (DM), and insulin resistance (IR) in young adults with overweight/obesity.

Methods: We studied 1507 US adults (BMI ≥25 kg/m^2, 20-49 y) in the National Health and Nutrition Examination Survey (NHANES) 2005-2006. Exclusion criteria included pregnancy, menopause, and glucocorticoid use. Skeletal muscle mass of both arms and legs [appendicular lean mass (ALM)] were measured by dual-energy x-ray absorptiometry. Relative sarcopenia was defined as low ALM/BMI. MetS was defined per National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria. IR was defined as Homeostatic Model Assessment (HOMA-IR) >50th percentile. Using sex-stratified regression models adjusted for age, race and physical activity, we tested whether relative sarcopenia was associated with MetS, DM, and/or IR. Effect estimates (OR) are reported per standard deviation (SD) change in ALM/BMI.

Results: Age was a negative, and physical activity a positive, determinant of ALM/BMI. Non-Hispanic Blacks had higher, and Hispanics had lower, ALM/BMI than non-Hispanic Whites. MetS was present in 21% of participants, and DM in 7%. The odds of MetS was 67% higher for each SD decrease in ALM/BMI in men [OR 1.67 (1.37-2.27), p=0.002]. The odds of DM was nearly three-fold higher for each SD decrease in ALM/BMI in men [OR 2.78 (1.49-5.0), p=0.001]. In participants without DM, the odds of IR was two-fold higher for each SD decrease in ALM/BMI in men [OR 2.0 (1.43-2.86), p=0.001]. None of these relationships were significant in women [MetS OR 1.15 (0.84-1.56), p=0.38; DM OR 1.11 (0.7-1.75), p=0.66; IR OR 1.35 (0.93-1.96), p=0.12]. Lower ALM/BMI was associated with higher odds of MetS in White and Hispanic, but not Black, men [White men OR 1.75 (1.22-2.56), p=0.002; Hispanic men OR 2.0 (1.01-3.7), p=0.03; Black men OR 1.14 (0.71-1.79), p=0.60]. Lower ALM/BMI was associated with relatively higher odds of DM in White and Hispanic compared to Black men [White men OR 3.03 (1.06-9.09), p=0.05; Hispanic men OR 2.94 (1.22-7.14), p=0.02; Black men OR 1.69 (1.14-2.56), p=0.01]. Lower ALM/BMI was associated with higher odds of IR in White men, but not Hispanic nor Black men, without DM [White men OR 2.33 (1.45-3.7), p=0.0004; Hispanic men OR 1.55 (1.0-6.29), p=0.16; Black men OR 1.56 (0.95-2.5), p=0.08].

Conclusion: In conclusion, relative sarcopenia (lower ALM/BMI) is a risk factor for MetS, DM, and IR in young overweight/obese men, but not women, and is a stronger risk factor for White than Hispanic or Black men. Relative sarcopenia may be an underappreciated mechanism linking overweight/obesity to cardiometabolic risk, especially in young White men. Prospective studies are needed to determine whether relative sarcopenia predicts incident cardiometabolic disease, including DM, over time. Understanding sex and racial differences in the relationship between relative sarcopenia and cardiometabolic risk may yield important insights into sex and racial disparities in cardiometabolic disease. In addition, identifying young adults with overweight/obesity who are at higher risk for cardiometabolic disease has the potential to significantly reduce long-term morbidity and mortality by offering targeted prevention and treatment strategies to reduce cardiometabolic risk.

Table 1. Clinical Characteristics

	Male (n=842)	Female (n=665)
Age		
20-29 y, n (%)	241 (29%)	202 (30%)
30-39 y, n (%)	293 (35%)	206 (31%)
40-49 y, n (%)	308 (36%)	257 (39%)
Race		
Hispanic, n (%)	258 (31%)	202 (30%)
Non-Hispanic Black, n (%)	210 (25%)	203 (31%)
Non-Hispanic White, n (%)	343 (41%)	233 (35%)
Cardiometabolic Risk		
Metabolic Syndrome, n (%)	176 (21%)	136 (20%)
Type 2 Diabetes, n (%)	58 (7%)	55 (8%)

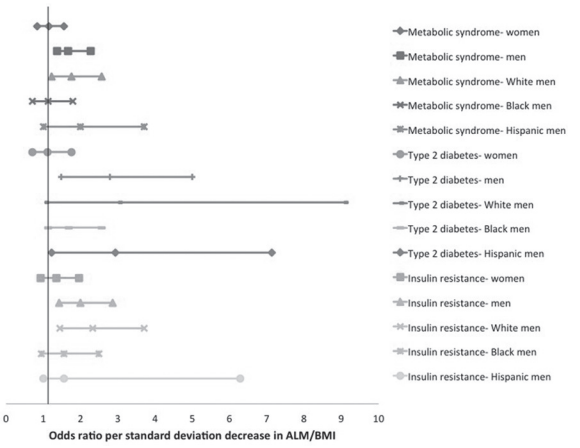

Figure 1. Associations between relative sarcopenia [lower appendicular lean mass (ALM)/ BMI] and prevalence of metabolic syndrome, type 2 diabetes, and insulin resistance (defined as HOMA-IR >50th%ile) in gender-stratified groups, as well as race-stratified groups in men only. Forest plot shows the odds ratio and respective 95% confidence intervals.

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Randi Schuster, PhD, Psychiatry

Memory Deficits are Reversible with Sustained Cannabis Abstinence among Cannabis Using Adolescents

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Introduction: Cannabis use in adolescence is widespread, and rates are likely to increase further as more states move toward creating legal markets for recreational and medicinal cannabis. Although several studies show neurocognitive dysfunction among adolescents within a few days of last cannabis use, it is unclear for what duration these deficits persist. Reversibility of neurocognitive dysfunction with abstinence would support a putative causal impact of cannabis on brain functioning. Additionally, a better understanding of the chronicity of neurocognitive recovery following cessation of cannabis use is critical in determining potential effects on academic functioning for the majority of adolescent regular users who do not use cannabis daily.

Methods: Eligible participants (N=88) were otherwise healthy adolescents, aged 16 to 25. Participants were randomized 2:1 to either to four weeks of cannabis abstinence achieved with a contingency management (CM) intervention (MJ-Abst; n=62) or non-contingent monitoring, matched for contact time, with no abstinence requirement (MJ-Mon; n=26). MJ-Abst participants earned incentives based on a two-track system for attendance and abstinence, with escalating denominations for both attendance and abstinence to encourage study retention and achievement of longer periods of continuous abstinence. Cannabis abstinence was indexed by self-reported non-use and by progressively decreasing 11-nor-9-carboxy-delta9-tetrahydrocannabinol (THCCOOH) concentration in urine. All participants completed 5 cognitive assessments using the Cambridge Neuropsychological Test Automated Battery (CANTAB) that occurred at baseline (prior to any change in cannabis use), and weekly for four consecutive weeks. Attention was indexed with the Attention Switching Task (AST) and the Rapid Visual Information Processing Task (RVP). Memory was measured with the Delayed-Matching-To-Sample Task (DMS), Verbal Recognition Memory Task (VRM), and the Spatial Span Task (SST). All primary outcome variables were converted to z scores based on the overall group means and standard deviations at baseline, when all participants were not abstinent. Z scores within each test were averaged at each time point and separately by group to create test score composites and averaged within domain at each time point and separately by group to created attention and memory composites.

Results: Of the 62 participants randomized to the four-week CM protocol, 53 (85.5%) participants maintained biochemically-confirmed 30-day continuous abstinence. There was a main effect of time [$F(4,88) = 13.80$, $p < 0.0001$] on attention, but group and the group by time interaction were not significant [*p-values* > 0.55]. Attention improved in both groups from baseline to week 1 [MJ-Abst: $\beta = 0.29$, $t(88) = 5.42$, $p < 0.0001$; MJ-Mon: $\beta = 0.23$, $t(88) = 3.16$, $p = 0.002$], from week 1 to week 2 in MJ-Mon participants [$\beta = 0.16$, $t(88) = 2.20$, $p = 0.03$], and from week 2 to week 3 in MJ-Abst participants [$\beta = 0.10$, $t(88) = 2.07$, $p = 0.04$]. There was a significant main effect of abstinence status on memory [$F(1,88) = 10.75$, $p = 0.002$], such those who were abstinent from cannabis had better memory performance overall than those who were not abstinent [$\beta = 0.22$, $t(88) = 3.28$, $p = 0.002$]. The main effect of time and the group by time interaction were not significant [*p-values* > 0.77]. Only MJ-Abst exhibited an improvement in memory functioning from baseline to week 1 [$\beta = 0.26$, $t(88) = 5.60$, p

< 0.0001]. There was no change in performance at all other time points across group [*p*-values >0.36]. MJ-Abst performed significantly better than MJ-Mon at week 1 [β = 0.26, t(88) = 3.43, p = 0.0009], week 2 [β = 0.19, t(88) = 2.25, p = 0.03], and week 3 [β = 0.25, t(88) = 2.83, p = 0.006]. For all three memory tasks, there was a main effect of time [SSP: $F(4,88) = 5.01$, $p = 0.001$; DMS: $F(4,88) = 4.54$, $p = 0.002$; VRM: $F(4,88) = 2.52$, $p = 0.047$], indicating that performance improved as study week progressed. Group and the group by time interaction terms were not significant for either SSP or DMS [*p*-values >0.09]. For the VRM, there was a main effect for group [$F(1,88) = 8.65$, $p = 0.004$]. MJ-Abst performed better than those who did not stop cannabis use overall [β = 0.45, t(88) = 2.94, p = 0.004] and at week 1 [β = 0.60, t(88) = 3.45, p = 0.0009], and there was a trend for better performance among MJ-Abst at weeks 2 [β = 0.38, t(88) = 1.93, p = 0.056], 3 [β = 0.42, t(88) = 1.95, p = 0.05], and 4 [β = 0.42, t(88) = 1.83, p = 0.07]. Memory performance improved from baseline to week 1 only in MJ-Abst [β = 0.24, t(88) = 2.36, p = 0.02]. The effect of VRM was driven by an effect on initial encoding, rather than delayed recall.
Conclusion: Findings support an adverse but likely reversible effect of regular cannabis use among adolescents on certain aspects of cognitive functioning. Cannabis abstinence is associated with improvements in memory, specifically an improvement in the ability to learn new information, and this improvement occurs in the first week following discontinuation of use. Cannabis abstinence is not associated with improvements in attention. Future studies are needed to determine whether these results reflect 1) a specific adverse impact of cannabis on memory functioning, or 2) deficits in attention that take longer to recover. Additionally, future studies should also recruit a non-using cohort to determine the clinical significance and potential functional impact of the observed memory improvement.

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Carl E. Schwartz, M.D., Psychiatry

A High-reactive Temperamental Profile In 4 Month-Old Infants Predicts Reduced Amygdala Volume and Increased Amygdala Reactivity In Adults

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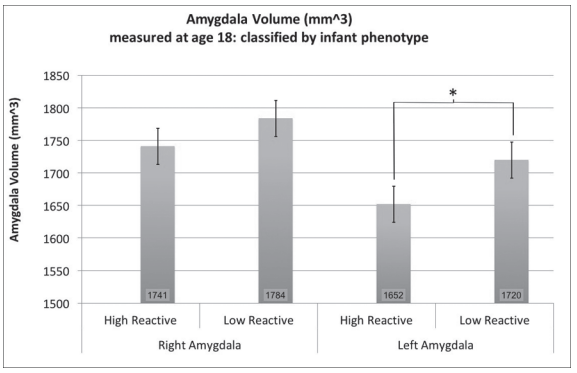
Introduction: High-reactive (HR) infants at 4 months of age show vigorous limb activity, arching of their back, and crying to unfamiliar visual, olfactory, and auditory stimuli. Low reactive (LR) infants show both low motor activity and low vocal distress to the same stimuli. HR infants are predisposed to show behavioral inhibition (BI) at two years of age.
Methods: Amygdala volume was determined with MRI in 135 adolescents (age 18.20 ± 0.07), who had been HR (n=55) or LR (n=80) infants. Effects of infant classification (HR, LR) on left and right amygdala volume in adulthood were analyzed with a MANOVA, with for age, sex, handedness, and ICV as covariates.
Results: Left amygdala volume in young adults who had been HR (1652 ± 20 mm3) was smaller than in those subjects who had been LR infants (1720 ± 25 mm3; F(1,118) = 4.7, p=0.03). The difference in the right amygdala was in the same direction (HR 1741 ± 24 mm3 vs. LR 1784 ± 20 mm3) but did not reach statistical significance (p=0.16).
Conclusion: Infant phenotypes observed in the first months of life predicted differences in amygdala volumes in the brains of young adults 18 years later. Reduced amygdala volumes have been reported in generalized social anxiety and major depression. Infant high-reactivity and BI are risk factors that predispose to those same outcomes. The volumetric differences reported in cross-sectional studies of anxiety disorders and depression could be attributable to a shared phenotype rooted in early infancy that cuts across traditional diagnostic categories.

Stimuli and behavioral responses used to determine infant phenotypes			
Order	Stimulus	Behavior Observed	Phenotype
1	Smiling mother + eye contact for 1 minute	Vigorous Limb Activity	High-Reactive
2	Audio of 8 sentences (unfamiliar voice)	Back-arching	
3	Series of mobiles: 3 types x 3 trials	Crying	
4	Cotton swab next to nostril (alternating water and butyl alchohol)		
5	Audio of nonsense syllables: 3 syllables x 3 trials each		
6	Popped balloon	Low motor Activity	Low-Reactive
7	Smiling mother + eye contact for 1 minute	Low vocal distress	

Stimuli used to determine infant phenotypes. At 4 months of age, subjects were categorized as either High-Reactive or Low-Reactive depending on behavior observed during a series of experimental stimuli shown here.



Right and left amygdala volumes measured in 135 subjects, grouped according to the same subjects' behavioral classification at 4 months old. High-reactive infants demonstrated significantly smaller left amygdalae than their low reactive counterparts at 18 years of age ($F(1,118) = 4.7$, $p=0.03$). The differences seen in the right amygdala were in the same direction, but did not reach statistical significance ($F(1,118) = 1.99$, $p=0.16$).

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Jennifer Searl, MS, Performance Analysis and Improvement/Practice Improvement

Ensuring PCP Panel Accuracy Post Epic

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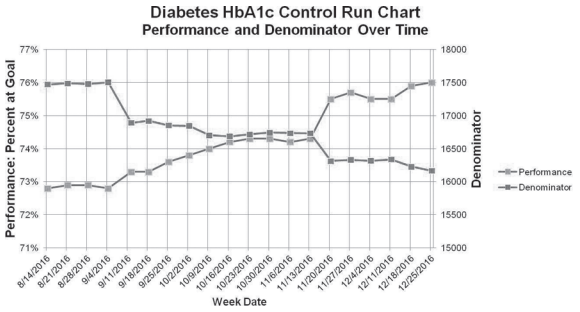
Introduction: After implementation of a new EHR (Epic) and a change in PCP attribution methodology, the denominator for MGH's ambulatory quality measures increased dramatically. The PCP field in Epic was converted from multiple legacy EHRs and was prone to over-attribution. This left MGH with an unreliable denominator for our quality measures. TIn response, we decided that by December 31, 2016, 100% of MGH PCP panels will be reviewed for misattribution by Population Health Coordinators to help improve the accuracy of our registries and the validity of our quality performance reporting.
Methods: Population Health Coordinators ran Epic 'Panel Attribution' report for each PCP in their practices and performed chart reviews. They removed: - Patients who hadn't been seen in > 5 years - Patients who had never been seen in practice and had no upcoming appintment -Deceased patients -Misattributed resident patients They consulted with PCPs on who hadn't been seen in 3-5 years and either: - Sent letter to patient requesting appointment -Removed patient from panel -Kept patient on panel
Results: 100% of PCP panels were reviewed. Dedicated review removed 16,613 patients from MGH denominator. This led to improved performance across all of our quality measures. More importantly, MGH primary care panels are now accurate.
Conclusion: PCP attribution data will likely be unreliable in transition to EPIC and a one-time clean-up effort is necessary. Panel Attribution report provided reliable way to assess accuracy of PCP panel. However, the manual review process was extremely time-intensive. We are concerned that maintenance of accurate PCP panels will require ongoing manual review. PHS should consider limitations on who can adjust the Epic PCP field or an algorithm to help aid ongoing panel maintenance.



Practice	# of pts remove
APF	343
Back Bay	2,116
Beacon Hill	1,313
BMG	498
Charlestown	1,250
Chelsea 100	348
Chelsea 151	893
Downtown	1,023
Everett	550
IMA	1,746
MG West	1045
MGMG	374
North End	1,000
PCA	920
PC Boston	65
Revere Broadway	805
Revere Adult	920
Revere Med/Peds	200
Senior Health	204
Women's Health	1,000
Total:	**16613**

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Ayla Senay, BS, Emergency

A ketamine-based package for procedural sedation in low-resource settings

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Introduction: Five billion of the world's 7.5 billion people do not have timely access to emergency or essential surgical care when needed, and lack of anesthesia services is a primary barrier. In response to this "anesthesia gap", the authors previously designed the evidence-based package, Every Second Matters for Emergency and Essential Surgery - Ketamine (ESM-Ketamine) TM for use by mid-level non-anesthetist clinicians when no anesthetist was available. The use of ESM-Ketamine evolved in an organic way such that providers have been using it for procedural sedation services and not just for emergency operations. This study analyzes the ESM-Ketamine package in support of painful procedures at the Siaya County Referral Hospital (SCRH) in Western Kenya.

Methods: This study was a sub-analysis of a multi-institution prospective case series. All painful procedures supported by the ESM-Ketamine package at the SCRH were analyzed. The institution's four ESM-Ketamine providers were interviewed in a semi-structured fashion.

Results: Between February 24, 2015 and February 6, 2017, the ESM-Ketamine package supported 163 painful and operative procedures at the SCRH, all of which were performed outside of the operating theatre. Mean ketamine dose was 2.7 mg/kg (range: 1.3 – 10.0) per procedure. Hallucinations or agitation treated with benzodiazepines and brief oxygen desaturation

occurred in 19 (11.7%) and one (0.6%) case, respectively. Four provider interviews demonstrated six themes: patient benefits, provider and facility benefits, care for similar patients prior to ESM-Ketamine implementation, provider and patient perceptions, challenges, and suggestions for improvement.
Conclusion: Implementation of the ESM-Ketamine package at the Siaya County Referral Hospital appeared to decrease wait times, improve quality of care, reduce pain and decrease costs associated with painful procedures.

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Jeehye Seo, Ph.D., Psychiatry

Fear and Extinciton Memory Network in individuals with Primary Insomnia and Good Sleepers

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Introduction: Healthy sleep promotes normal emotional regulation as well as the consolidation of emotional memories. Acute sleep disturbance and insomnia, on the other hand, is pervasive following a variety of stressors and traumatic events. Insomnia can be characterized as a predisposing factor for the development of anxiety and traumatic stress disorders – disorders characterized by abnormalities in fear conditioning and extinction. To date, there are no known functional neuroimaging studies examining fear conditioning and extinction in persons with primary insomnia. Differences in brain activations in the fear expression and extinction networks of persons with primary insomnia (vs healthy controls) may be due to chronic sleep disturbances, and the further study of these differences may help further define the relationship between sleep disturbances, emotional memory, and psychiatric disorders.
Methods: Nineteen subjects diagnosed with primary insomnia (14 female, mean age=29.3, SD=12.0) and nineteen healthy controls (14 female, mean age=29.3, SD=11.7) underwent two weeks of sleep monitoring with wrist actigraphy and sleep diaries before completing a validated 2-session fear conditioning and extinction protocol, with continuous skin conductance recording (SCR), inside a 3T fMRI scanner. During Session 1, responses were established to 2 differently colored lamps (CS+) but not a third (CS-) using a mild electric shock (Fear Conditioning). One CS+ (CS+E) but not the other (CS+U) was then extinguished (Extinction Learning). Twenty-four hours later, at Session 2, all 3 CSs were presented (Extinction Recall). Changes in neural activation (BOLD signal) among fear and extinction ROIs were examined across fear conditioning, fear extinction, and extinction recall. Neural regions that showed a difference in task-based activation between groups – persons with primary insomnia (PI) vs good sleepers (GS) – were identified. Beta values were extracted from these regions and were compared to various measures, including sleep efficiency (Actigraph-based and Diary-based) and Extinction recall index (ERI). Whole brain images were acquired using a conventional 32-channel head coil in a 3T MRI imaging device (Siemens Medical Systems). MATLAB and SPM8 were used to process BOLD images and perform statistical analyses on fMRI data. Regions of interest (ROIs) were selected based on functional activations observed during responding in regions specified in previous literature on neural networks of fear conditioning and extinction (including past studies using this protocol). Areas of the brain examined for activations were restricted to known regions of the fear and extinction circuit including the amygdala, dACC, insula, vmPFC (including rACC), and hippocampus. To examine neural activation patterns seen within groups, one sample t-tests were conducted on the BOLD signal from each ROI in various contrasts. Group level whole-brain analyses were conducted using two sample t-tests to investigate the differences in fear network ROI activation between PI and GS subjects during fear conditioning and fear extinction learning. Pearson correlation analyses were used to determine the correlations between psychophysiological data and brain activations related with fear conditioning, extinction learning and recall processing. All statistical analyses were performed using the SPSS software (SPSS, Inc., Chicago, IL, v.20) and statistical significance was set at $P < 0.05$.
Results: At the end of fear conditioning, both PI and GS exhibit activations in neural regions associated with the fear conditioning process. At the end of extinction learning, GS exhibit enhanced activity in both the fear expression network and in parts of the fear extinction network. PI, on the other hand, demonstrate limited activational changes in these regions. In the recall of a previously extinguished fearful stimulus (CS+E) compared to an unpaired stimulus (CS-), PI relative to GS exhibited enhanced activation of neural regions associated with a fear response. These increased activations of the fear expression network were correlated with poorer sleep efficiency and poorer extinction recall (as evidenced by SCR). In the recall of CS+E compared to an unextinguished stimuli (CS+U), PI relative to GS demonstrated greater activation in the vmPFC, a region involved in fear extinction memory.
Conclusion: PI and GS both demonstrated significant activity in neural regions involved in the expression of conditioned fear. These activations may indicate that both PI and GS have "learned" fear conditioning. By the end of fear extinction learning, GS participants showed increased activity in both the fear expression and fear extinction networks. This synchronous activity in both networks may be indicative of the dynamic competition between the fear conditioning memory (e.g., a certain color is "dangerous") and the newly learned fear extinction memory (e.g., that same color is "safe.") In contrast, PI show

very limited changes in neural activation in either network by the end of extinction. In early recall, PI demonstrate activation in both the fear expression and fear extinction networks. This pattern is roughly similar to the neural activations seen in GS at the end of fear extinction learning. Taken together, these results may indicate that PI demonstrate delayed processing and activation of fear memories. Indeed heightened activation of fear response regions in early recall was correlated with impaired (SCR) recall as well as poorer sleep efficiency. These data suggest that individuals with sleep disturbances may experienced delayed processing of fear extinction memories compared to individuals with healthy sleep. Further research is required to determine the extent to various sleep measures affect the consolidation of these and other emotional memories.

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Veri Seo, BA, Medicine - Mongan Institute for Health Policy

Individual Insurance Market Enrollees with Chronic Conditions: Finding Physicians Who Accepted Their Plan

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Introduction: Access to physicians depends both on local physician supply and insurance network constraints. Many areas of the country currently face physician shortages, particularly for mental health (MH) specialists; moreover, many MH compared to non-MH providers do not accept insurance. The Affordable Care Act expanded enrollment in individual market (nongroup) insurance plans; however, difficulty finding needed providers could be even greater in these types of plans, which frequently have narrow provider networks in large part to control spending and premiums. We examined the frequency with which individual market enrollees reported difficulty finding a primary care provider (PCP) or specialists who accepted their insurance, and whether there were differences for enrollees with MH and non-MH chronic conditions.

Methods: We conducted a telephone and web-based survey among a random sample of 2,103 adults enrolled in individual market plans in California, both on- and off-exchange, in 2014. Respondents reported whether they had any chronic conditions, defined as asthma/other lung disease, diabetes, heart disease or stroke, heart failure, cancer, arthritis, hepatitis/other liver disease, depression/other mental illness, or HIV. Respondents also reported whether they had a lot, some, or no difficulty finding a PCP or specialists in 2014 who accepted their insurance, or if they had not yet looked for either. Because of a priori concerns about limited MH specialist supply, we differentiated between those with and without MH chronic conditions. We used multivariate logistic regression to examine the association between having a MH vs. other chronic condition and the likelihood of having difficulty finding a PCP, adjusting for patient characteristics such as age, sex, race, education, income, self-rated health status, and prior insurance status. We repeated these analyses for difficulty finding specialists.

Results: Overall, 59% of respondents did not have any of the specified chronic conditions; 25% had at least one non-MH condition; 8% had only a MH condition; and 7% had both non-MH and MH conditions. Among those who looked for a PCP or specialists (84% and 69% of respondents, respectively), 35% and 43% reported having difficulty finding the needed provider. Respondents with a MH condition were more likely to report difficulty finding a PCP (38%) and specialists (49%) compared to those with non-MH conditions (32% and 36% for finding a PCP and specialists, respectively) and those with both MH and non-MH conditions (27% and 40%). After adjusting for patient characteristics, respondents with a MH condition were significantly more likely to report difficulty finding specialists compared to those with non-MH conditions (OR=2.0, 95%CI: 1.2-3.3); there were no significant differences in difficulty finding a PCP.

Conclusion: In this population of individual market enrollees in California, many had difficulty finding PCPs and specialists who accepted their insurance. Enrollees with chronic conditions faced more difficulty finding a specialist than in finding a PCP; having difficulty finding a specialist was particularly pronounced for those with mental illness. While limiting the provider network represents a potentially valuable tool for insurers to manage medical spending, attention is needed to ensure adequate access to both PCPs and specialists for those with more complex medical needs. Additional resources to assist enrollees as they choose their health plans or physicians could help mitigate this concern.

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Gloria Serena, PhD, Pediatrics

Pleiotropic Effect of Pt-Gliadin on Primary Human Macrophages is Regulated by Epithelium Released Factors in Celiac Patients

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Introduction: Celiac disease (CD) is an autoimmune enteropathy triggered by the ingestion of gluten in genetically predisposed individuals. CD pathophysiology is characterized by an increased number of intraepithelial and lamina propria immune cells. Studies on murine primary macrophages and monocyte/macrophage cells lines have shown that gliadin induces the secretion of a broad spectrum of pro-inflammatory cytokines. However studies on human primary macrophages are scarce. Monocytes derived macrophages are plastic cells that can differentiate into either a pro-inflammatory (M1) or an anti-inflammatory (M2) subtype depending on the surrounding microenvironment. Our study aims to determine which subtype of macrophages is induced by gliadin and how the cross-talk between immune cells and the epithelium contributes to this effect.
Methods: We isolated $CD14^+$ monocytes from whole blood samples of healthy controls (HC) or CD patients and differentiated them into macrophages by adding 50 ng/ml of M-CSF (macrophage colony stimulating factor) to the culture medium. To determine the effect that gliadin has on macrophages, at day 6 the cells were cultured in medium alone or with 1 mg/ml of previously pepsin and trypsin digested gliadin (PTG). Macrophages cultured with 10 ng/ml of MCSF and 20 ng/ml of IL4 were used as positive control for M2 condition, while macrophages cultured with 20 ng/ml of IFNγ and 100 ng/ml of LPS served as positive controls for the M1 condition. To study the cross talk between epithelium and immune cells, the macrophages were cultured using as medium the supernatant of CaCo2 cells previously cultured with medium alone or with 1mg/ml PTG. Supernatant of CaCo2 cells stimulated with 100 ng/ml of LPS was used as a positive control for the stimulation. Real time PCR was used to measure the expression of M1 (IL6, IP10, TNFα) and M2 cytokines (TGFβ and CCL22).
Results: Our data show that PTG has a pleiotropic effect on the macrophages of both groups of subjects by triggering both M1 pro-inflammatory and M2 anti-inflammatory cytokines profiles. Production of CCL22, IL6, TNFa increased upon stimulation with PTG, while TGFb and IP10 production decreased. Interestingly the macrophages cultured with the CaCo2 supernatants showed a different outcome for some of the cytokines. The production of CCL22 was significantly reduced in HC macrophages cultured with the supernatant of CaCo2 + PTG as compared to the macrophages cultured in medium + PTG ($p<0.05$). Conversely, in CD patients the supernatant from CaCo2 cultures + PTG triggered a significantly higher production of CCL22 as compared to the medium condition ($p<0.05$) and to the HC subjects as well ($p<0.05$). The supernatant of CaCo2 + PTG induced also an increased production of TNFα in CD patients compared to the macrophages cultured with medium and to the macropohages cultured with supernatant from non stimulated CaCo2 ($p<0.05$). The production of other cytokines did not seem affected by the culture with supernatant derived from CaCo2 cultures.
Conclusion: Our data show that PTG has a pleiotropic effect on human primary macrophages. Furthermore these experiments suggest that factors released by epithelial cells contribute to the effect that gliadin has on human monocytes derived macrophages and that immune cells from CD patients respond differently to these factors than cells from HC subjects. The high production of CCL22 triggered on CD patients by CaCo2 supernatant + PTG is compelling given the role that this chemokine has on recruiting Treg cells and that CD has been associated with and increased number of Treg cells. Furthermore the higher production of TNFα that we measured in the CaCo2 + PTG condition underlines that macrophages from CD patients respond differently to factors released by PTG-stimulated epithelium as compared to HC and suggest that CD cells are more prone to produce pro-inflammatory cytokines. In conclusion from our data we can infer that the cross talk between epithelium and immune cells represents an important component of the CD pathogenesis. Further studies are deemed to investigate the exact mechanisms and factors by which the epithelium contributes to the immune cells differentiation and function and how this may lead to the loss of tolerance in genetically predisposed individuals.

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Kristen A. Severson, Medicine

Vasopressin administration is associated with higher lactate levels in intensive care unit patients with sepsis

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Introduction: Sepsis and septic shock affect more than a million Americans annually and have been found to contribute to as many as 1 in every 2-3 hospital deaths. Serum lactate is generally accepted as a marker of the severity of sepsis and is predictive of mortality, but the impact of vasopressin administration on serum lactate level is not fully understood. The objective of this study was to examine the relationship of vasopressin use on serum lactate levels in patients with sepsis.
Methods: The study is a retrospective analysis of electronic heath records using the Medical Information Mart for Intensive Care or MIMIC database to analyze change in serum lactate values during admission to the intensive care unit (ICU). MIMIC-III contains electronic patient records from the Beth Israel Deaconess Medical Center in Boston, Massachusetts between 2001 and 2012. Adult patients in the medical or surgical ICU with sepsis as identified via the criteria of Angus et al. (2001) were included. Patients were required to have a serum lactate measurement up to six hours prior to or within six hours of arrival to the ICU and a subsequent measurement approximately 24 hours later. The exposure of interest was vasopressin administered between hours 3 and 18 of the ICU stay. A matched study using covariates concerning disease severity, demographics, laboratory values, vital signs, and interventions was performed.
Results: 1,173 patients, 152 of whom received vasopressin, met the inclusion criteria. The matching resulted in 102 patient pairs. The change in serum lactate was analyzed both as a continuous and a binary variable. Patients receiving vasopressin had a median increase in serum lactate of 0.3 mmol/L, while patients not receiving vasopressin had a median decrease in serum lactate of 0.7 mmol/L (p-value < 0.001). Patients receiving vasopressin had a 6.6-fold increase in their odds of having an increase in serum lactate as compared to patients who did not receive vasopressin (OR 6.6; 95% CI 3.0-15, p-value < 0.001). A sensitivity analysis was performed using norepinephrine as the relative time index for serum lactate measurements and the results did not significantly change.
Conclusion: Administration of vasopressin is associated with increased serum lactate values in ICU patients with sepsis. Given the prognostic significance of serum lactate among septic patients, the relationship between vasopressin use and serum lactate levels merits further study.

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Peng Shao, PhD, Dermatology

Brillouin ocular analyzer detects biomechanical changes in corneal tissues in the early stages of keratoconus and after corneal crosslinking: clinical study findings

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Introduction: The biomechanical properties of the cornea have been implicated in the onset and progression of keratoconus (KC). The ability to measure corneal biomechanics may critically enhance our ability to detect KC earlier and more accurately. However, this hypothesis has not been fully tested clinically owing to the dearth of techniques sensitive enough to obtain biomechanical metrics. To address this need, we have previously developed a novel optical technique based on Brillouin light scattering spectroscopy for non-contact, in vivo biomechanical characterization. The objective of the present study is to test the clinical potential of this technology in KC patients and to develop biomechanics-based diagnostic metrics, particularly for the detection of KC in early stages and for the evaluation of corneal stiffening following treatment with corneal collagen crosslinking (CXL).
Methods: Studies were performed at Massachusetts General Hospital (MGH) and the Institute for Refractive and Ophthalmic Surgery (IROC) in Zurich, Switzerland, according to IRB-approved protocols. Recruited study subjects include 44 subjects with normal corneas (age 39.2+/-14.0 y/o), 62 subjects diagnosed with KC of varying severity (Stage I: n = 25, 36.1±11.7 y/o; Stage II: n = 9, 45±13.1 y/o; Stage III: n = 4, 47.3±12.3 y/o; Stage IV: n = 8, 45.6±15.9 y/o), and 37 KC patients treated with CXL in the past 4 years (age 34.6±10.8 y/o). KC grading into four stages was made according to the Amsler-Krumeich Classification criteria, which is based on Scheimpflug corneal topography. Custom-built Brillouin optical microscopy

systems using near infrared light were used to obtain Brillouin-shift maps of the corneas. Various biomechanical metrics based on the measured Brillouin shifts were analyzed, and statistical correlation with the degree of KC and with the elapsed time after CXL was measured.
Results: We found that the most sensitive metrics for the diagnosis of KC were related to regional variations within the corneas of each individual. In normal corneas, the Brillouin shifts were spatially uniform. By contrast, in both early and advanced stages of KC (I to IV) the Brillouin shifts at the thinnest point or cone regions were significantly ($p < 0.001$) lower than the values in the corneal periphery, indicating focal weakening. The regional difference correlates with the severity of KC and effectively cancels out the patient-to-patient variability in Brillouin shift, which makes average Brillouin shift an ineffective metric for the detection of early stage KC (I and II). CXL-treated corneas (n=16, 34.6 ± -10.8 y/o) showed higher Brillouin shifts ($p < 0.05$) compared to untreated, early-stage KC corneas (n = 8, 25.6 ± 10.7 y/o), in modest correlation with the elapsed time after CXL (r^2=0.16; n=30, 29.7 ± -12.2 y/o, 24 males).
Conclusion: The Brillouin biomechanics-based metrics revealed a clear difference between healthy and mild (stage I) KC corneas and between CXL-treated and non-treated KC corneas. These remarkable findings support the potential of Brillouin imaging for diagnosis and post-therapy monitoring of KC patients and warrants further clinical studies to test how these metrics enhance the early screening and management of KC patients.

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Benjamin G. Shapero, PhD, Psychiatry

Associations between Amygdala Connectivity, Psychopathology, and Implicit Negativity Bias

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Introduction: Psychiatric disorders commonly co-occur and share phenotypic clinical features. In parallel, multiple risk factors and neurobiological correlates are common across psychiatric disorders, yet research in this area is more limited. Cognitive biases, or misinterpretations of environmental cues, are associated with the many forms of psychopathology and represent a transdiagnostic mechanism for the onset of psychiatric disorders. Research supports the association of cognitive biases with anxiety, depression, and psychosis. Consistent with this body of behavioral studies is neuroimaging evidence for common changes in brain function across these conditions. In particular, the function and connectivity of the amygdala has been shown to be altered across disorders. However the relationship between cognitive biases and shared abnormalities in brain function remains unknown. The goal of the current study was to examine whether cognitive biases represent a transdiagnostic correlate in symptom presentation and to examine their neural correlates. We hypothesized that a higher cognitive bias will be associated with symptoms and changes in amygdala connectivity. We then explored whether cognitive biases are a mechanism through which amygdala connectivity abnormalities lead to psychiatric symptoms.
Methods: Mental health screenings were conducted at local Boston universities between 2010-2013. Participants completed symptoms measures of depression, anxiety, and psychosis. A subset of subjects (N=66; Mage=19.6; 74% female) underwent functional neuroimaging scans and completed a behavioral task that assessed the tendency to misattribute neutral words as negative (negativity bias). All subjects participated in a MRI scanning session (Siemens 3T Tim Trio), which included two resting-state BOLD scans (each 6.2 min) during which subjects were instructed to keep their eyes open and blink normally. Standard preprocessing techniques were applied using in-house scripts.
Results: Whole-brain regression revealed that a negativity bias was positively correlated with connectivity between the amygdala and: 1) visual cortex and 2) dorsomedial prefrontal cortex; and negatively correlated with connectivity between the amygdala and: 1) the left and right temporal cortex, 2) precuneus, and 3) ventromedial prefrontal cortex (Figure 1). Regression models indicate that individuals with a higher negativity bias had higher levels of anxiety (t=3.06, p<.01), depression (t=2.18, p<.05), and psychotic-like symptoms (t=1.99, p<.05). A multivariate model revealed that only anxiety symptoms remained significant after controlling for co-occurring symptoms (t=2.00, p<.05). A bootstrapping approach was used to measure whether the negativity bias mediated the associations between amygdala connectivity and symptoms. In one instance, the negativity bias fully mediated the relationship between amygdala connectivity and symptom levels (Figure 2).
Conclusion: Prior research has reported commonalities in clinical presentation and risk factors across many psychiatric disorders. The current study builds on this research, identifying that an automatic bias to misattribute negative meaning to neutral stimuli is associated with symptoms of depression, psychosis, and anxiety. However, negativity bias may be most strongly associated with anxiety symptoms, consistent with literature indicating that those with anxiety disorders have a heightened attention towards threat. In addition, this study found that the negativity bias is associated with a pattern of amygdala connectivity that facilitates fear processing. Specifically, the positive correlation between the negativity bias and amygdala- dmPFC

connectivity and negative correlation with amygdala-vmPFC connectivity can be interpreted in light of evidence that the amygdala-dmPFC pathway is centrally involved in generating fear-related responses, whereas the amygdala-vmPFC pathway, and local circuitry within the temporal cortex, plays a key role in fear inhibition. This indicates that individuals with patterns of amygdala connectivity that facilitates fear processing show a greater bias to misattribute negative meanings to neutral information, and in turn, are more likely to experience symptoms. Thus, negativity bias may be one mechanism that explains the association between abnormalities in regions of the brain involved in emotional function and poor psychiatric outcomes. This study provides new insight into how and why negativity biases lead to psychiatric problems.

Figure 1.

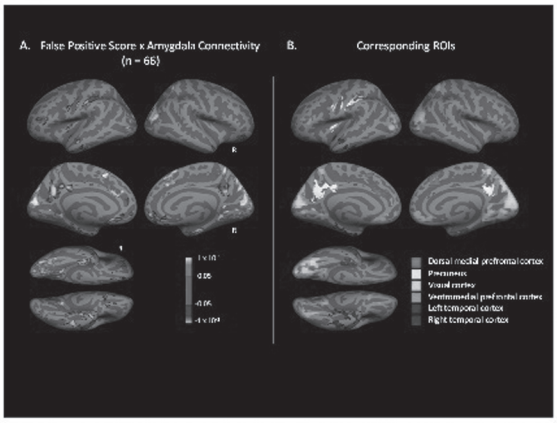
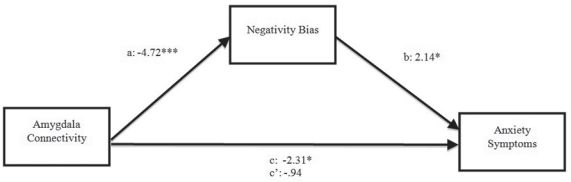


Figure 2. Mediation analysis



Note: Amygdala connectivity presented in this figure indicates the amydala-left temporal cortex connectivity

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Shilpa Sharma, MD, Medicine

Managing the Risk for Sudden Cardiac Death in Patients with Spontaneous Coronary Artery Dissection

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Introduction: The incidence of spontaneous coronary artery dissection (SCAD), defined as non-traumatic, non-iatrogenic, and non-atherosclerotic separation of the coronary artery wall, is rising with increasing awareness and advances in diagnostics. Optimal management of SCAD patients remains unclear because recommendations are primarily based on observational series. Furthermore, there is no published literature on implantable cardioverter-defibrillator (ICD) therapy for SCAD patients. ICD therapy is sometimes used in SCAD patients especially after sudden cardiac death (SCD) but the benefits are unclear and placement has risks.

Methods: We initiated the Massachusetts General Hospital (MGH) SCAD registry to gather contemporary data regarding the clinical characteristics and management of SCAD patients. We aimed at assessing the risks of SCD and use of ICD therapy in SCAD. At the time of data analysis, our registry included 102 patients, all presenting to MGH with SCAD or referred after a SCAD episode. Data was gathered through a combination of reviewing records from the patient's SCAD hospitalization, initial consultation with a cardiologist at MGH, and patient surveys. We compared clinical variables between SCAD patients with and without SCD. We also report data on ICD placement and initial outcomes after ICD placement.

Results: Of the 102 patients, 14 experienced SCD. Table 1 summarizes clinical characteristics of SCAD patients who experienced SCD (n=14) versus those who did not (n=88). Patients with SCD were more likely to be peripartum, tobacco users, present with STEMI, receive an ICD, and had higher incidence of repeat SCAD. Seven of the 102 patients underwent ICD placement. 5/7 ICD placements were for secondary prevention. 2/7 were for primary prevention, one for inducible ventricular tachycardia and the other for recurrent episodes of non-sustained ventricular tachycardia. During mean follow-up of 3.5 years, 1 patient received an ICD discharge for supraventricular tachycardia and 1 patient had significant ICD complications. Four additional individuals received life vests, most commonly in the setting of low ejection fraction. All 4 patients had normal ejection fractions within 2 months resulting in discontinuation.

Conclusion: SCAD complications are alarmingly prevalent with an estimated 10-year rate of major adverse cardiovascular events of 47% and SCAD recurrence rate of 29%. Therefore, ICD therapy in SCAD patients intuitively makes sense and, as seen from our registry, is sometimes employed in practice. However, the risk-benefit ratio of ICD therapy in SCAD is unclear. Guidelines currently support ICD therapy only for secondary prevention in the absence of reversible causes and for primary prevention in patients with persistently low LVEF. SCAD lesions usually heal spontaneously and ejection fraction is often

preserved or recovers shortly after acute presentation. Therefore SCAD is not a condition that technically fits within guidelines for ICD therapy. Furthermore, SCAD patients possibly could decrease their risk of SCD by avoiding future pregnancies and quitting smoking, risk factors associated with SCD in our study. Finally, preliminary outcomes from our SCAD registry suggest that complications of ICD therapy may outweigh benefits. Our dataset is currently limited in size and follow-up, but brings awareness about ICD therapy in SCAD, an issue that needs to be addressed given that patients with SCD are not well represented in the current SCAD literature, despite lack of data on ICD therapy in SCAD it is sometimes employed in practice, and the risks of ICD therapy may outweigh benefits in SCAD patients.

Table 1. Baseline Characteristics, Predisposing Factors, Management, and Outcomes of Patients presenting with SCAD, with or without Cardiac Arrest

Category	Variable	Patients with Cardiac Arrest (n=14)	Patients without Cardiac Arrest (n=88)	P value
Baseline Characteristics	Age, years	44 ± 11	48 ± 10	0.19
	Female Sex	13 (93%)	75 (85%)	0.45
	Hypertension	6 (43%)	25 (28%)	0.28
	Hyperlipidemia	1 (7%)	27 (31%)	0.07
	Obesity	1 (7%)	15 (17%)	0.35
	Tobacco Use	7 (50%)	17 (19%)	**0.01**
	Presentation with STEMI	11 (79%)	32 (36%)	**<0.001**
	EF, %	44 ± 12	53 ± 13	0.13
Predisposing factor/trigger	Emotional Stressor	4 (29%)	31 (35%)	0.63
	Physical Stressor	6 (43%)	23 (26%)	0.20
	Peripartum	4 (31%)	8 (11%)	**0.05**
	Hx of Gestational HTN, Pre-eclampsia, Eclampsia	5 (38%)	12 (16%)	0.06
Management	Conservative management	7 (50%)	56 (64%)	0.33
	PCI	7 (50%)	30 (34%)	0.25
	CABG	0 (0%)	3 (3%)	0.49
	ICD Placed	5 (36%)	2 (2%)	**<0.001**
Outcomes	30 Day re-admission	4 (29%)	10 (12%)	0.11
	Repeat SCAD Occurrence	3 (21%)	5 (6%)	**0.04**
	Mortality	0 (0%)	0 (0%)	NA

Values are n (%) or mean ± SD. Peripartum state and hx of gestational HTN/pre-eclampsia/eclampsia was relevant for female patients only (n=13 for patients w/ cardiac arrest and n=75 for patients without cardiac arrest). 30 day re-admission was only available for n=83 patients without cardiac arrest.

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Cristina Shea, Anesthesia, Critical Care and Pain Medicine

Conventional thermal versus water-cooled genicular nerve radiofrequency lesioning (RFL): a retrospective chart review.

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Introduction: Persistent knee pain affects 25% of adults >55 year old in a given year. When conservative therapies fail, genicular nerve radiofrequency lesioning (RFL) may be a promising therapy to provide long-term pain relief. In this outpatient procedure (requiring only local anesthetic), electrodes that release radiofrequency waves are used to thermally ablate the sensory nerves transmitting pain from the knee. While a number of case series and randomized controlled trials have reported sustained improvement in pain scores following genicular nerve RFL, there is significant heterogeneity in technique among these studies. It is unknown is whether conventional thermal RFL (CT-RFL) or water-cooled RFL (WC-RFL), which results in larger radius lesions, leads to better outcomes, as there have been no head-to-head comparisons of outcomes. We aimed to fill this knowledge gap by conducting a retrospective chart review of patients treated in our clinic with either CT-RFL or WC-RFL for chronic knee pain.

Methods: We conducted a retrospective chart review to examine outcomes in patients treated in our clinic with CT-RFL (n=35) vs. WC-RFL (n=31) between 1/2014 and 12/2016. Our primary outcome was improvement in Visual Analog Scale (VAS) pain score from baseline at follow-up visits within the year following the RFL procedure. Monthly post-procedure VAS scores from clinic notes during the year following the RFL were collected. If multiple VAS scores were found in a given follow-up month for a given participant, these scores were averaged to yield one pain score per the month. All statistical analyses were conducted using R V3.3.2. Random intercepts models with patient as a random effect were utilized to examine VAS scores over time. The models apply baseline pain score as a reference for each patient and were adjusted for age, gender and prior knee surgery on the procedure knee. The models allow for inclusion of VAS scores from multiple procedures for the individuals who underwent multiple RFLs. All hypothesis testing was two-tailed with significance interpreted as $p<0.05$.

Results: A total of 47 individuals received genicular nerve RFLs during the study period. Of these patients, 38 underwent a single RFL, while 9 underwent multiple RFLs (5 underwent 2 RFLs, 2 underwent 4 RFLs, and 2 underwent 5 RFLs). In total, data from all 66 procedures was used in the modeling. There were no follow-up pain scores for 10/66 procedures due to loss to follow-up. VAS scores were significantly reduced from baseline (mean=6.66, SD=1.36) by 1.46 points at one month

follow-up (95% CI: 0.6 to 2.3, p=0.001), 2.22 points at two months follow-up (95% CI: 1.4 to 3.1, p=<0.001), and 1.24 points at six months follow-up (95% CI: 0.1 to 2.4, p=0.035) but were not significantly reduced at other months during the one year follow-up time period. Individuals treated with CT-RFL appeared to have slightly lower VAS scores over time than individuals treated with the WC-RFL, however the difference was not statistically significant (mean difference=0.73, 95% CI: -0.14 to 1.59, p=0.116). Four post-procedure complications were reported in the CT-RFL group vs. none in the WC-RFL group, though this difference was not significant (p=0.10, two-tailed Fisher's exact test). The major limitation of this study was lack of available follow-up VAS scores, which increased as follow-up month increased.
Conclusion: There were no significant differences in follow-up VAS scores or rates of complications between the CT-RFL and WC-RFL group. Interpretation and generalization of these findings is difficult due to limited follow-up data, likely with bias in which patients returned to report VAS scores. Further studies with larger sample sizes are needed to address whether magnitude of pain relief, duration of pain relief, and complication rates differ between CT-RFL and WC-RFL techniques.

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Sarah D. Simeone, DPT, Neurology

To Stand or Not to Stand: Feasibility and Associations of Supported Standing Interventions in Children with Spinal Muscular Atrophy (SMA) I and II

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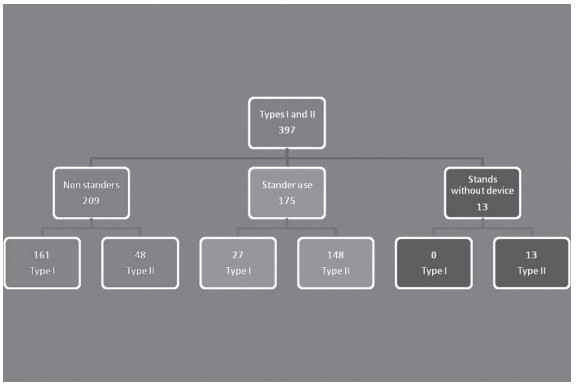
Introduction: Supported standing is advocated for children with SMA given potential benefits for spinal alignment, bone density, muscle length, GI function, pulmonary health and cognitive and social engagement. Although evidence supports standing interventions in children with cerebral palsy and muscular dystrophy, the feasibility, predictors and impact of stander use in SMA remain unclear. Therefore, we used a large SMA natural history dataset to characterize stander use in SMA types I/II and to identify factors associated with standing interventions.
Methods: 397 children with SMA (188 type I, 209 type II) age 1 month-12 years at enrollment were followed from 2004-2015 as part of a multi-site natural history study. Predictor variables targeted for exploratory analyses included SMA type, *SMN2* copy number, ventilatory support, and motor performance (Test of Infant Motor Performance Screening Items/TIMPSI and Modified Hammersmith Functional Motor Scale/MHFMS). The outcome variable of interest was stander use, which was examined two ways: 1) Stander use versus no stander use and 2) Meaningful stander use (defined as use ≥ 3x/week) versus no/limited stander use (none, occasionally, 1-2x/week). Logistic regression with backwards selection was used to examinethe extent to which predictors were associated with stander use. Odds ratios with 95% confidence intervals were calculated.
Results: The prevalence of stander use was 44% overall, with 14% of children with SMA type I and 71% of children with type II using a stander. Stander use was reported as young as 6 months (type II) and 8 months (type I). TIMPSI and MHFMS total scores were not associated with stander use. SMA type II (odds ratio, 0.043; 95% CI, 0.02-0.08; p=<0.0001; n=384), but not *SMN2* copy number, and use of respiratory support (odds ratio, 0.363; 95% CI, 0.17-0.64; p=0.0012; n=384) were associated with stander use. Head control at 12 months of age, indexed by TIMPSI Item 14-Head Rotation, was positively associated with meaningful standing (use of stander ≥ 3x/week). For every 1 point increase in item score, a nearly two-fold increase in the odds of stander use was apparent (odds ratio, 1.9; 95% CI, 1.2-3.1; p =.01; n=64).
Conclusion: Supported standing represents an important functional bridge between sitting and independent standing/walking and should be considered as an intervention for children with SMA Type I and II by the end of the first year. Early head rotation control (near 1 year of age) was associated with meaningful stander use (≥3x/week), suggesting a possible early predictor of successful supported standing. The association between use of non-invasive respiratory support (BiPAP, CPAP) between ages 9-24 months and stander use could relate to a "proactive care" approach by families that prioritizes both interventions, OR proactive respiratory care may improve standing tolerance. By establishing feasibility and providing initial evidence for factors that may predict stander use in SMA, this work sets the stage for future research addressing the therapeutic impact of standing. The ability to establish and predict successful stander use by children with SMA will allow us to better explore the therapeutic benefits of standing in prospective studies. With new SMA drug therapies (e.g. Spinraza™), significantly improved developmental potential is possible, including independent standing and walking in children with SMA types I and II. Prioritizing early weight bearing and supported standing may be critically important in helping children with SMA achieve maximal functional potential. Further exploration of optimal positioning, load, duration and potential benefits including bone mineral density, respiratory and GI health, and functional motor outcomes of standing is needed. Additional factors that may impact feasibility and tolerance of standing, including health literacy, social supports and stresses, socioeconomic status and general health of child and family should be incorporated into predictive models in future studies.

Associations between potential predictors and stander use

Likelihood of meaningful stander use (≥ 3x/week)				
Variable	Fixed Effect (Beta)	Odds Ratio	95% CI	P-value
Head Rotation (Item 14-TIMPSI)	B = 0.648	1.912	(0.162, 3.143)	0.011
Likelihood of any stander use				
Variable	Fixed Effect (Beta)	Odds Ratio	95% CI	P-value
Respiratory Support	B = -0.561	0.363	(0.166, 0.642)	0.0012
SMA Type (Ref Type 2)	B = -1.571	0.043	(0.022, 0.084)	<0.0001



Flow diagram of subjects (n=397) by SMA type and standing status (never stood, used stander, or stood independently)

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Ajay Singh, MD, Radiology

Imaging of Necrotizing Fasciitis of the upper extremity: Distinguishing cellulitis from Necrotizing fasciitis

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Introduction: Cellulitis is a relatively common infection of the skin and subcutaneous tissues which may comprise up to 14% of emergency visits and 7% of hospital admissions. Necrotizing fasciitis (NF) is a potentially fatal, uncommon infection of the soft tissues which can be difficult to diagnose and distinguish from cellulitis. We aim to analyze and compare imaging findings of cellulitis and NF of upper extremity in our large academic medical center.

Methods: This is a HIPAA compliant, IRB approved, retrospective study of cases imaged between 2003 and 2017. Imaging database of our institution was searched for all cases of upper extremity cellulitis and NF. The reference standard for the diagnosis was surgery, and/or clinical follow-up. Medical records were reviewed for patient clinical and imaging variables.

Results: A total of 50 cases were included (mean age: 44.5, 25 male 25 female). 15 cases had proven NF by surgery and 35 cases had cellulitis proven surgically and/or clinical follow-up. CT was acquired in 60.0% of NF cases (9/15) and 74.3% of cellulitis cases (26/35). Other imaging modalities used were MRI, plain radiograph, and US. Air was significantly more common present in NF compared with cellulitis (53.3%, 8/15 and 20.0%, 7/35 respectively) (p=0.04). Other common associated imaging findings with NF were subfascial fluid (n=6) and fascial thickening (n=8). NF was significantly more likely to be fatal compared with cellulitis (20.0%, 3/15 and 0%, 0/35 respectively) (p=0.02). All cases of cellulitis with soft tissue air, had history of recent incision and drainage, penetrating trauma, IV drug use, injection of steroid or immunization. Skin thickening and superficial subcutaneous tissue involvement was seen in all cases of cellulitis who had CT or MR. Soft tissue abscess was seen more commonly in cellulitis (31.4%, 11/35) compared with NF (26.7%, 4/15). Cellulitis cases who had soft tissue abscess, had significantly more intramuscular edema (66.7%, 6/9), compared with the cases without abscess (13.6%, 3/22) (p=0.007).

Conclusion: Soft tissue air, fascial thickening and subfascial fluid collection are significantly more commonly seen in the NF than cellulitis. Majority of soft tissue air in cellulitis cases can be explained by history of recent trauma, IV drug use, immunization, incision and drainage, and injection.

Diagnosis	Total cases	Mean Age	Male: Female (Ratio)	Imaging modalities used for detection				# Of cases with air in soft tissue (%)	# Of cases with abscess in soft tissue (%)	# Of deceased cases due to infection/sepsis
				US (%)	Plain Radiograph (%)	CT (%)	MR (%)			
Necrotizing Fasciitis	15	51.6	5:10 (0.5)	0 (0.0%)	4 (26.7)	9 (60.0%)	2 (13.3%)	8 (53.3%)	4 (26.7%)	3 (20.0%)
Cellulitis	35	41.1	20:15 (1.3)	3 (8.6%)	2 (4.6%)	26 (74.3%)	5 (14.3%)	7 (20.0%)	11 (31.4%)	0 (0.0%)
Total	50	44.5	25:25 (1.0)	3 (6.0%)	6 (12.0%)	35 (70.0%)	7 (14.0%)	15 (30.0%)	15 (30.0%)	3 (6.0%)

Cellulitis cases	Abscess +	Abscess -	Total
Intermuscular edema present	6	3	9
Intermuscular edema absent	3	19	22
Total	9	22	31

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Nikhil Sobti, Surgery - Plastic & Reconstructive

Analysis of Acellular Dermal Matrix Efficacy in Prosthesis-Based Breast Reconstruction

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Introduction: Breast cancer is the most common cancer to affect women in the United States. Acellular dermal matrix (ADM) has become one of the most commonly applied medical devices for breast reconstruction. Staged breast reconstruction utilizes ADM to support breast tissue expander (TE), which is filled over the patient's recovery period until exchanged for an implant during a second operation. Despite the availability of outcome-based research exploring the safety of ADM in the context of immediate implant-based breast reconstruction, no studies have been conducted to evaluate the clinical efficacy of ADM as soft tissue reinforcement. We hypothesize that ADM use allows for enhanced tissue support following breast reconstruction, and its efficacy can be objectively measured as higher initial fill volume at mastectomy, decreased number of expander fills, and shorter interval between exchange of tissue expander for implant.

Methods: IRB approved retrospective chart review was conducted to identify consecutive tissue expander-based procedures performed at a tertiary academic medical center over 12 years. Univariate and binomial regression analyses were conducted to compare patient characteristics and clinical endpoints between ADM and non-ADM groups.

Results: Mean initial tissue expander fill volume was significantly higher in the ADM group when compared to non-ADM (180.8 ± 150.0 v. 45.8 ± 74.4, respectively, p = 0.00). Normalizing for final implant size, which serves as a surrogate for body composition, the ADM group exhibited significantly higher perioperative fill (0.33 ± 0.24 v. 0.11 ± 0.16, p = 0.00). Patients who underwent ADM-based reconstruction also experienced fewer TE expansions (5.0 ± 2.0 fills v. 6.7 ± 2.6 fills, p = 0.00) and shorter duration between TE placement and implant exchange (5.4 ± 3.6 months v. 7.0 ± 4.9 months, p = 0.00) (Table 1). Post-operative complication rates were similar between groups. In addition, we observed a collinear trend between ADM use and direct-to-implant reconstruction procedures at our institution during the time period of the study (Figure 1).

Conclusion: We present the first study to evaluate efficacy of ADM in immediate tissue expander mediated breast reconstruction. We used clinically objective endpoints of tissue expander initial volume and number of fills as outcome measures of efficacy. Our results suggest that ADM use is associated with greater initial fill and fewer visits for expansion following immediate-TE placement when compared to non-ADM procedures. Furthermore, we detected a collinear relationship between ADM use and number of direct to implant (DTI) procedures at our institution, without need for expansion and protracted staged reconstruction. This work serves as a framework for future studies evaluating ADM efficacy and can guide the manufacture of novel medical technologies.

Table 1 – Comparison of efficacy outcomes between ADM and non-ADM groups.

Outcome	ADM	Non-ADM	p
Primary Efficacy Endpoint			
Mean IFV ± SD (mL)	180.8 ± 150.0	45.8 ± 74.4	0.00*
Mean IS ± SD (mL)†	497.9 ± 150.6	439.6 ± 152.8	0.82
Ratio, IFV:IS, ± SD†	0.33 ± 0.24	0.11 ± 0.16	0.00*
Secondary Efficacy Endpoint			
Mean no. fills ± SD	5.0 ± 2.0	6.7 ± 2.6	0.00*
Mean TE-implant exchange interval ± SD (m)	5.4 ± 3.6	7.0 ± 4.9	0.00*

IFV, initial fill volume; IS, implant size; m, months.

*Statistically significant ($p<0.05$).

†Data unavailable for cases in which tissue expander was prematurely removed due to post-operative complication.

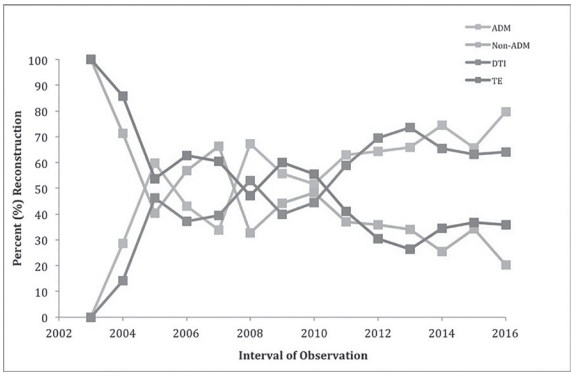

Figure 1. Evaluation of ADM-based breast reconstruction at a tertiary academic medical center between 2003 and 2016. The increased use of ADM over time correlates with the rise of DTI, suggesting that the reinforcement capability of ADM allowed for implantation of the terminal prosthesis.

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Alexander A. Sousa, Pathology

Engineered CRISPR-Cpf1 Genome-Editing Nucleases with Improved Targeting Range

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Introduction: Genome editing nucleases have been widely adopted for research applications as they enable permanent sequence-specific modification of genes. While these nucleases have shown immense promise, one notable limitation of CRISPR nucleases is the restriction of targeting to sites that contain a particular protospacer adjacent motif (PAM). This requirement can limit implementations that require precise targeting. CRISPR-Cpf1 nucleases bear a number distinctive features relative to the commonly used *Streptococcus pyogenes* Cas9 (SpCas9) nuclease, including: recognition of an extended T-rich PAM, catalysis that generates 5'-overhangs of 3 to 5 nucleotides in length, and the requirement for only a single short ~40 nt crRNA. We have previously characterized two Cpf1 orthologues from *Acidaminococcus sp. BV3L6* and *Lachnospiraceae bacterium ND2006* (AsCpf1 and LbCpf1, respectively). We found that these enzymes can robustly function for genome editing in a variety of human cell types and that they possess high genome-wide specificities. However, both AsCpf1 and LbCpf1 recognize a PAM of the form TTTV (where V is any nucleotide other than T), substantially limiting targeting relative to the NGG PAM motif utilized by SpCas9.

Methods: To improve the targeting range of CRISPR-Cpf1 nucleases, we examined high-resolution 3D-crystal structures of AsCpf1 to identify amino acid residues that contribute to PAM recognition. Rationally directed mutations at residues that lie within 10 angstroms of the PAM nucleotides identified a subset of amino acids whose substitution might be expected to alter PAM recognition. We generated Cpf1 variants harboring various combinations of mutations at these positions and characterized their on-target activities and genome-wide specificities in human cells.

Results: Using a structure-guided approach, we rationally engineered AsCpf1 variants that we predicted to have an expanded ability to recognize PAM motifs beyond the canonical TTTV PAM of the wild-type enzyme. Testing of various combinations of mutations in human cells identified one AsCpf1 variant that has activity equivalent or better than wild-type AsCpf1 on canonical TTTV and TTTT PAM sequences (Figure 1). Importantly, this AsCpf1 variant also shows robust activity on sites with PAMs of the form NTTN, TATN, and TTCN, sequences that are not efficiently cleaved by wild-type AsCpf1. This variant expands PAM recognition from TTTV to NWYN (where W is A or T, and Y is T or C), thereby increasing the targeting range by more than three-fold (Figure 1). Preliminary experiments suggest that these engineered AsCpf1 variants exhibit only a modest difference in specificity compared to wild-type AsCpf1. Finally, sequence alignment of CRISPR-Cpf1 nucleases reveals that residues important for altering PAM recognition are conserved across Cpf1 orthologues, suggesting that our approach may be generalizable to additional Cpf1 nuclease orthologues (e.g., LbCpf1 and others).

Conclusion: Our results demonstrate that both natural and engineered forms of CRISPR-Cpf1 nucleases are robust and useful enzymes, and that our AsCpf1 PAM variants expand targeting range by more than three-fold. These findings should encourage broader implementation of these genome editing reagents for both research and therapeutic applications.

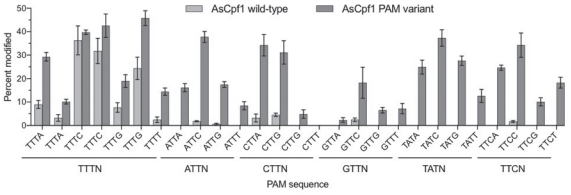

Figure 1. An engineered variant of AsCpf1 with improved targeting range.

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Jessica St. John, MBA, MPH, Dermatology

Location of skin lesions in Henoch-Schönlein purpura (HSP) and its association with renal involvement

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Introduction: Henoch-Schönlein purpura (HSP) is an immunoglobulin-A-associated small-vessel vasculitis characterized by immune-complex deposits, which commonly affect the gastrointestinal tract, joints, and kidneys. Clinically, patients with HSP may present with nonthrombocytopenic palpable purpura predominantly on the lower extremities, arthralgias, abdominal pain, and impaired renal function. Although less common in adults as compared to children, HSP has a more significant risk of systemic complications in adults (*i.e.*, gastrointestinal (GI) tract, joint, and renal involvement), most notably the risk of developing renal insufficiency. Although currently there is no clear efficacious treatment to prevent long-term sequelae. A significant amount of research on HSP has focused on determining predictors for systemic involvement in adults. Such predictors include the distribution of skin lesions, renal involvement around the time of diagnosis, as well as histopathologic findings. The definition of renal involvement has varied among studies. Moreover, some studies only evaluate renal data within the first 30 days of HSP diagnosis without accounting for baseline renal function prior to diagnosis as well as potential long-term sequelae. Alternatively, other studies with more rigorous methods of evaluating renal function are limited by the fact that they include only patients who have undergone renal biopsy, likely selecting a more severely-affected patient population. In this study, we present longitudinal data on renal function from 72 adult patients with skin-biopsy proven HSP using baseline renal function for comparison. We also examine distribution of skin lesions, presence of systemic symptoms, and conjugates found on direct immunofluorescence (DIF) of the skin biopsy specimens as predictive factors for renal and systemic involvement.

Methods: Using the Partners HealthCare searchable patient data system, Research Patient Data Registry (RPDR), we conducted a search using the terms "Henoch Schönlein purpura," "skin biopsy," and "vasculitis" of all adult patients seen at the Massachusetts General Hospital and its affiliated outpatient clinics and Brigham and Women's Hospital from January 1, 2000 to December 31, 2014. Summary statistics are provided with a mean, median, standard deviation, and range. Comparisons were made among DIF conjugates and the presence or absence of GI tract, joint, or renal involvement using chi-square tests. Age and creatinine were evaluated among categories with a two-sided t-test. A logistic regression analysis was performed evaluating long-term renal involvement while controlling for sex, age, and lesion distribution. Study data were collected and managed using REDCap electronic data capture tools hosted by Partners HealthCare.[9] Statistical analyses were performed using SAS software (version 9.4, SAS Institute, Inc., Cary, NC) and *P* values less than 0.05 were considered significant.

Results: Results of the statistical analysis revealed that the location of HSP lesions (upper and lower extremities only) trended towards significantly increasing the odds of having long-term renal involvement by 4.767 (P=0.067), controlling for sex, age, and baseline creatinine. Moreover, among men only, the location of lesions (upper and lower extremities only) significantly increased the odds of having long-term renal involvement by 6.55 (P=0.049), controlling for age and baseline creatinine.

Conclusion: We provide evidence that skin lesion distribution may be a predictive factor in long-term renal involvement, which may be critical for risk stratification and development of personalized diagnostics and therapeutics for HSP patients in the future. This study, among others, attempts to identify factors predictive of disease outcome with regards to HSP and renal disease. However, definitions of renal involvement and severity of disease at baseline are highly variable. We provide evidence that skin lesion distribution may be a predictive factor in long-term renal involvement. Moreover, we identify skin lesion distribution on the upper and lower extremities may be an indicator of long-term renal involvement. These findings require validation in future studies and, if confirmed, will be critical for risk stratification and development of personalized diagnostics and therapeutics for HSP patients. There is likely a selection bias among patients in this study due to their recruitment at two large academic hospitals in an urban setting. Many patients were even hospitalized for their care. However, one way in which this study may have more generalizability than others is the fact that it includes patients with HSP who have not had a renal biopsy. Several studies on predictive factors of outcomes in HSP include only patients who have undergone renal biopsies, thereby selecting those with renal disease severe enough to warrant a renal biopsy.[3,8] Such evaluations may be skewing our analysis of HSP and renal sequelae. Larger studies of patients with HSP and long-term renal data are needed to determine and evaluate the significance of potential predictive factors identified in HSP sequelae.

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Jessica St. John, MD, MBA, MPH, Dermatology

The successful use of cyclosporin A for Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in three pediatric patients.

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Introduction: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare medical emergencies characterized by widespread skin necrosis and risk of hemodynamic instability and sepsis. Estimated mortality rates for SJS and TEN are 5% and 30-50% respectively; these rates are much lower in children. The majority of SJS/TEN cases are caused by adverse drug reactions, though some may be due to infection (*e.g., Mycoplasma pneumoniae*). Mainstays of treatment for SJS/TEN include removal of the offending agent, supportive care, and appropriate wound care. Use of immunosuppressive agents such as corticosteroids and intravenous immunoglobulin (IVIg) is controversial. Neither treatment has an established clinical benefit and there have been reported associations with increased mortality. In contrast, cyclosporin A (CsA) use in SJS/TEN has been associated with dramatically arrested disease progression, increased reepithelialization, and reduced mortality.
Methods: We describe three pediatric patients seen at Massachusetts General Hospital diagnosed with SJS/TEN confirmed by skin biopsy, who were successfully treated with CsA with improvements seen in time to arrest of new lesions, reepithelialization, and duration of hospital stay.
Results: The average arrest time after CsA administration was 2.2 days (range 1.5-3) and average time to remission or reepithelialization was 13 days (range 10-15). The average length of stay in the hospital was 11.7 days (range 4-19).
Conclusion: Literature on the treatment of SJS/TEN in children is remarkably sparse, and what research does exist focuses on the treatment debate between corticosteroids and IVIg. This case series provides additional evidence that CsA is an efficacious treatment and suggests it may be used as a monotherapy in pediatric patients with SJS/TEN. Additional trials are needed to evaluate the safety and efficacy of CsA use in children. Nevertheless, CsA is associated with substantial clinical improvement in halting disease progression and fostering reepithelialization in patients with SJS/TEN and has a demonstrated safety profile. These results are promising and deserve further investigation.

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A Critical New Role for a Long Non-coding RNA (*RMST)* as a 'Master Regulator' of the Ontogeny of GnRH Neurons from Their Neural Crest Origins.

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Introduction: Genetic investigations in the human disease model of Kallmann Syndrome [KS] (anosmia + hypogonadotropism) has led to the discovery of several new genes that control the developmental biology of GnRH producing cells that ultimately govern all of mammalian reproduction. Taken together, however, these known KS genes explain only ~40% of its genetic architecture. While some chromosomal rearrangements have led to identification of select KS genes, to date their analysis has been limited. Recent development in next generation sequencing has allowed a more detailed analysis of such structural events that has begun to reveal novel findings pointing to the importance of long non-coding RNAs (LncRNA) in neurodevelopment. However, the biology of LncRNA's remains incompletely understood due in part to the difficulties of assessing their function *in vitro*. Consequently, the phenotypes of patients with mutations in LncRNAs can provide invaluable insights into their basic biology.
Methods: We analyzed the genome of a male patient with Kallmann Syndrome with a known *de novo* translocation between chromosomes 7 and 12 using jumping library based whole genome sequencing (WGS) to resolve the translocation breakpoint to a single base pair resolution. The position of the translocation breakpoints were confirmed with Sanger sequencing. Whole exome sequencing (WES) was used to search for mutations in known IGD genes. The patient's lymphocytes were

then transformed to both iPSCs and then neural crest cells. Levels of the LncRNA involved in the breakpoint, *RMST,* were tested with qPCR in both cell lines and compared to controls. *SOX10* and *SOX2* RNA-immunoprecipitation (RIP) were also performed to test the interaction between those genes.
Results: (i) WES revealed no LOF mutations in any known KS genes and only a heterozygous missense mutation in the leptin receptor gene (*LEPR*) was identified; this mutation was predicted to be benign (ii) WGS allowed the resolution of the translocation to base pair level, that revealed *only* the disruption of a LncRNA gene (*RMST)* on chr12:97,860,651- 97,860,653; (iii) iPSCs expressed <6%-18% of the total RMST levels of healthy iPSCs and NCs <20% of the *RMST* levels in the healthy NCs thus confirming loss of function (LOF) in *RMST*; (iv) While WT *RMST* levels increased during neural crest cell differentiation and directly bound *SOX2* and *SOX10* NC differentiation (NC cells biding *SOX2* and *SOX10*) was impaired in the patient's cells compared to controls. (v) when mutated in neural stem cells *RMST* LOF results in increase in *CHD7, SEMA3A and TUBB3 &* decrease in *MKRN3* levels, all known to affect GnRH neuronal ontogeny.
Conclusion: Taken together, this KS patient with an isolated LOF in *RMST* identifies a previously unappreciated role for this LncRNA, *RMST,* as a key early regulator of the ontogeny of GnRH cells from their neural crest origins and during their subsequent migration into the CNS. As such, it appears that *RMST* fulfills many of the roles of a 'master regulator' of GnRH neuronal ontogeny.

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Mark Stoltenberg, MD, Emergency

Palliative Care in Belize: Measuring cost savings through a retrospective cohort study

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Introduction: Palliative care is a medical specialty focused on the prevention and relief of human suffering—specifically the physical, emotional and spiritual burdens that patients and their families experience when facing serious or terminal illness. The global need for palliative care is immense. It is currently estimated that roughly 5.5 million terminal cancer patients and 1 million end-stage AIDS patients suffer without access to palliative care each year. Low and middle income countries (LMICs) bear a disproportionate share of this worldwide morbidity and mortality. In Belize, a small country of only 350,000 people in Central America, the primary provider of palliative care services for is the Belize Hospice and Palliative Care Association (BHPCF) which was founded by Dr. Beatriz Thompson in 2006 to respond to the palliative care needs of her country. Through a network of volunteer physicians, nurses and other non-medical personnel, the BHPCF has provided care to hundreds of seriously and terminally ill patients across Belize. However, because of limited financial, human and operational resources, the BHPCF has only been able to care for a small fraction of the population in need of palliative care services. From November 2015 to April 2016, the BHPCF received a small pilot grant from the Belize Ministry of Health, which enabled them to hire a full-time physician to lead home visits, and supervise the collection of patient data. This study was therefore conducted as a retrospective matched cohort study, which sought to better characterize the demographics of patients cared for by the BHPCF, as well as the potential cost savings achieved for the health system by decreasing hospital admissions.
Methods: Baseline data was gathered from in person surveys, biopsy reports, and the Belize Health Information System (BHIS—the universal EMR used across the country) for all patients admitted to the BHPCF home care service from November 1st, 2015 through April 30th, 2016. Baseline data included: age, gender, home address, primary diagnosis and date of admission to home care services. The number of home visits and date of death were documented by the BHPCF team. The BHIS was additionally used to retrospectively document all hospital admissions for the home care patients. Data from January 2015 to October 2015 was used as a comparative control.
Results: One hundred and ten patients were enrolled in the BHPCF home care program during the study period. The most common primary diagnoses included cancer (39%)), stroke (18%) and dementia (14%). Fifty-six (50.9%) of the patients were male and 54 (49.1%) female. Six hundred and thirty-eight home visits were made during the study period. Patients received a mean of 5.8 (range one to 22) visits over the 6-month study period. Thirty-nine (35.4%) patients died during the study period, 32 (29.1%) of whom died at home. There were 33 hospital admissions over the six months. During the 10-month control period (before being admitted to the BHPCF home care program) the same patient cohort underwent 139 hospital admissions. The savings to the health system for this cohort translated to $7,560 USD monthly and $90,720 annually.
Conclusion: This retrospective, matched cohort study suggests that that palliative home care may considerably lessen admission rates and associated costs.

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Daniela Suarez-Rebling, B.S., Emergency

Feasibility and experiences of an Acute Response Team in a rural community hospital in western Kenya: A report on the first 58 patients

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Introduction: Acute response teams (ART) have been established in many well-resourced hospitals around the world in order to optimize teamwork in emergency situations. Organized approaches to critical medical conditions lead to earlier intervention, higher quality care, and better patient outcomes. The ART at Sagam Community Hospital, a 70-bed general hospital in Luanda, Kenya, appears the first of its kind in a rural African setting. This paper reports on the Sagam Community Hospital ART responses to-date.

Methods: The Sagam Community Hospital ART was designed by defining nine positions: one Kenya family and emergency medicine resident (Team Leader), one medical officer doctor intern (MOI), two clinical officers (CO), two nurses, one transport nurse, one porter technician, and a customer care staff member. The ring of a loud bell, restricted for this use only, immediately triggered the ART to respond to the Emergency Care Center (ECC) resuscitation room. Any member of the hospital staff was given the freedom to trigger the ART for any inpatient or newly presenting patient, at any time, if they deemed a patient to be in an "emergency state". "Emergency states" were defined as level-one-priority for first time presenting patients (based on the Canadian Triage and Acuity Scale), and for patients recognized to be acutely decompensating on the wards. All ART patients were immediately transferred to the resuscitation room in the ECC. Detailed time-stamped resuscitation team data was collected real-time for each ART response. Team leaders filled out a 2-page survey immediately subsequent to completion of the ART response. The survey also asked for comments on any challenges.

Results: Between February 24, 2017 and July 10, 2017, the Acute Response Team (ART) was activated in support of 58 emergencies. 32 (55.2%) of the 58 were male and 26 (44.8%) female. Mean age was 36.7 (age range: 8 months- 80 years). Six of the 58 (10.3%) were inpatients and 52 (89.7%) newly presented to the ECC. 32 (61.5%) of the 52 newly presenting patients were admitted to the hospital. Seven (12.1%) of the 58 ART activations died and three were transferred to a higher level of care. Mean time from bell activation to patient stabilization was 36.1 minutes (time range: 1- 147 minutes). Nineteen (32.7%) of the 58 ART activations were for acute trauma. Among 54 responses, the mean Team Leader rating for overall quality of care was 8.3 (rating range: 6- 10) on a 10 cm Likert scale. The most common reported challenges included: "lack of medications and equipment", "equipment malfunctions", "lack of staff", and "communication breakdowns".

Conclusion: An acute response team was found to be feasible in a rural hospital in western Kenya. Acute response team leaders reported considerable challenges, yet, overall, they described a positive experience. Further research will seek to improve the ART model and understand its overall impact and opportunity for scale.

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Haoqi Sun, Neurology

How Old Is Your Brain? Predicting "Brain Age" from Large-Scale Sleep EEG

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Introduction: In the Big Data era, the combination of large clinical datasets and advanced machine learning supports a variety of novel research questions not easily addressed previously. We have curated a large database of overnight polysomnography (PSG) from the MGH Sleep Lab with full clinical annotations and multi-channel physiology. Subtle age-dependent changes in sleep EEG are well known, but have not been systematically explored in large datasets. We hypothesize that EEG during sleep can predict chronological age (CA). The deviation between the CA and predicted "brain age" (BA) may hold important clinical and mechanistic insights into the aging process and risk of age-related neurological disorders. To test this hypothesis, we predict BA from various EEG features using machine learning and compare with prediction using delta EEG power only (the strongest prior age-related feature). Importantly, the outliers provide a window into which clinical factors potentially account for deviations from chronological age.

Methods: We analyzed EEG from 4,330 adult patients during diagnosis time from our retrospective IRB-approved registry. 102 EEG features were extracted from each 30-second epoch, including frontal, central and occipital leads. These features were then averaged for each sleep stage, resulting in 510 EEG features (5 sleep stages) for each patient. We implemented

automatic relevance determination (ARD, a sparse Bayesian method) to predict age based on these features. To compare, we also predicted BA using only delta EEG power (0 -- 4Hz) in N2 and N3 (the two deepest sleep stages).
Results: Figure 1A shows the prediction performance, with Pearson correlation of 0.75 ($p < 0.01$) for ARD. Since ARD is a Bayesian method, it also provides the uncertainty in age prediction, where the average standard deviation is 7.6 yrs. By comparison, in Figure 1B, the Pearson correlation based on delta power alone is 0.54, showing that our algorithm provides substantial improvement. Importantly, sleep apnea severity was uncorrelated with the deviation between BA and CA. In fact, no PSG-derived clinical sleep metric had a correlation R-value beyond +/-0.2. Interestingly, the strongest positive correlation with BA - CA was BMI (0.12).
Conclusion: The results show that, in a heterogeneous adult clinical population, we can predict the "brain age" based on EEG features with far stronger correlation than using delta power alone. It is intriguing to speculate that deviations from chronological age, both in the younger and older directions, may have clinical implications for age-related cognitive performance or neurodegenerative disorders. Future works include relating the deviations to other important clinical factors such as medicine, and analyzing the stability of the brain age prediction on the same patient over time.

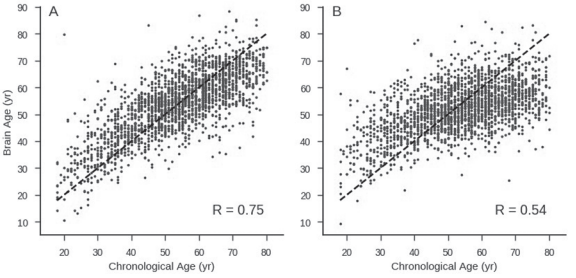

Figure 1. The actual chronological age vs. predicted brain age. The number indicates Pearson correlation. (A) Prediction using 102 EEG features in each sleep stage; (B) Prediction using delta band (0 -- 4Hz) features in N2 and N3.

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Variation in the echocardiographic surveillance of primary mitral regurgitation

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Introduction: Clinical outcomes after surgical treatment of mitral regurgitation (MR) are worse if intervention occurs after deterioration of left ventricular (LV) size and function. Trans-thoracic echocardiographic (TTE) surveillance of patients with MR is indicated to avoid adverse ventricular remodeling. Overly frequent TTEs can impair patient access and reduce value in care delivery. This balance between timely surveillance and over-utilization of TTE in valvular disease provides a model to study variation in the delivery of health care services. We investigated patient and provider factors contributing to variation in TTE utilization, and hypothesized that variation was attributable to provider practice even after adjustment for patient characteristics.
Methods: We obtained records of all TTEs from 2001-2016 ordered at a large echocardiography laboratory. The outcome variable was time interval between TTEs. We constructed a mixed-effects linear regression model with the individual physician as the random effect in the model, and used intra-class correlation coefficient (ICC) to assess the proportion of outcome variation due to provider practice.
Results: Our study cohort was 55,773 TTEs corresponding to 37,843 intervals ordered by 635 providers. The mean interval between TTEs was 12.4 months, 17.0 months, 18.3 months, and 17.4 months for severe, moderate, mild, and trace MR respectively, with 20% of providers deemed over-utilizers of TTEs, and 25% under-utilizers. Provider factors of specialization and experience were significantly correlated with intervals between TTEs.
Conclusion: We concluded that there is substantial variation in follow-up intervals for TTE assessment of MR, despite risk-adjustment for patient variables, likely due to provider factors.

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Martin Taylor, Pathology

A Conserved Distal Lung Regenerative Pathway in Acute Lung Injury

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Introduction: Biopsy is rarely performed in patients with the acute respiratory distress syndrome (ARDS), even though it may lead to changes in management and improve survival. The most common histologic finding in ARDS is diffuse alveolar damage (DAD), present in approximately half of patients, and can be understood as a common pathway resulting from a variety of insults. Although the stages of human DAD have been defined morphologically for decades, the mechanistic basis of repair following acute lung injury remains poorly understood. While improved tools have led to a burgeoning understanding of lung regeneration in mice, it is not yet known how these insights may be relevant to acute lung injury in humans.
Methods: Routine clinical testing, pathology, immunohistochemistry, and electron microscopy. All surgical lung wedge biopsies and autopsies with a diagnosis of DAD at the Massachusetts General Hospital (MGH) from 2011-2016 were reviewed as control cases. Cases with a background of cancer or extensively fibrotic lung disease were excluded. Ordinal regression and associated p-values were computed using R statistical software (version 3.3.2) with the MASS (version 7.3-45) and ordinal (version2015.6-28) packages.
Results: We report in detail two cases of fulminant idiopathic acute lung injury requiring extracorporeal membrane oxygenation in previously healthy young adults with ARDS, one of whom required lung transplantation. Biopsies showed diffuse alveolar injury with a striking paucity of alveolar epithelial regeneration, rare hyaline membranes, and diffuse contiguous airspace lining by macrophages. We term this novel constellation "diffuse alveolar injury with delayed epithelization" (DAIDE). Additionally, mirroring data from murine models of lung injury/regeneration, we identified peribronchiolar basaloid pods (previously described as "squamous metaplasia") and ciliated bronchiolarization in these patients and in 39% of 57 historical cases with diffuse alveolar damage (DAD). Bronchiolarization appeared late in illness ($p=0.00053$) and in an identical anatomical distribution to the peribronchiolar basaloid pods.
Conclusion: The diagnosis of DAIDE is a distinct pattern from DAD and appears to portend a poor short term prognosis; these findings require further characterization. In these patients, we demonstrate a common and clinically relevant human disease correlate for murine models of severe acute lung injury. We provide evidence that peribronchiolar basaloid pods and bronchiolarization are related spatially and temporally and likely represent overlapping sequential stages of the response to severe distal airway injury.

Figure 1

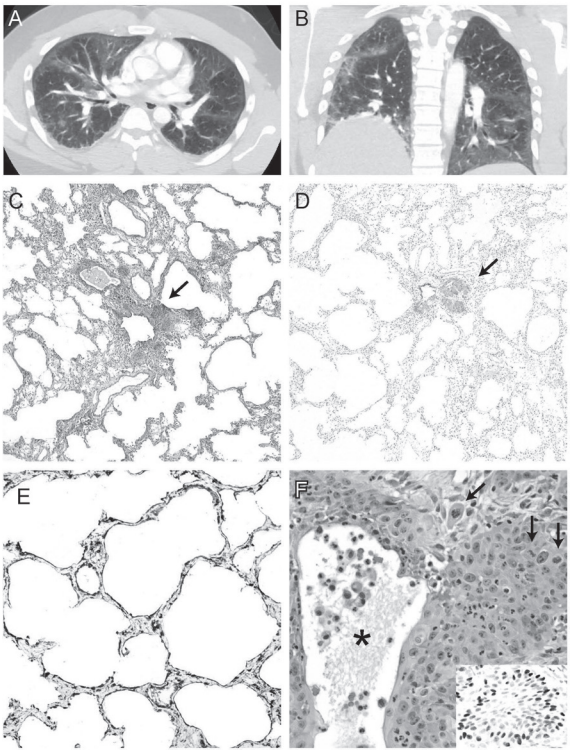

Figure 1. Alveolar epithelialization in DAIDE Case 1. A, B) Chest radiograph showing diffuse pulmonary infiltrates. C) Lung biopsy H&E stain at low magnification demonstrate diffuse alveolar denudation and peribronchiolar basaloid pods (arrow). Hyaline membranes are rare and non-conspicuous and the lung interstitium is mildly thickened. D) The absence of alveolar epithelium in Case 1 is highlighted by the lack of cytokeratin cellular immunostaining, whereas the peribronchiolar basaloid pods are cytokeratin positive (arrow); control cases of DAD (not shown) are diffusely cytokeratin positive, with staining in regenerative and residual pneumocytes as well as hyaline membranes. E) CD163 immunohistochemistry demonstrates macrophages contiguously lining denuded alveoli. F) Peribronchiolar basaloid pods at high power (H&E stain) shows nests of atypical cells with rapid proliferation (arrows: mitoses) surrounding and contiguous with a bronchiole (star: lumen).

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Distinct psychopathological correlates of delusional ideas in a non-clinical population: implications for the mechanisms of psychosis

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Introduction: Although psychosis is typically approached clinically as a single biological process related to abnormal dopamine neurotransmission (Laruelle M. et al., 1999; Kapur S. et al., 2005), it is in fact comprised of a number of distinguishable symptom types, including hallucinations and delusions, with additional subtypes (e.g., auditory and visual hallucinations, and persecutory, religious and many other types of delusional beliefs) within these broader symptom categories. Different psychotic symptoms do not always co-occur clinically, and some have been linked to distinct cognitive mechanisms and changes in brain function (Blackwood N.J. et al., 2001; Bell V et al., 2006). The mechanisms underlying the phenomenological differences among psychotic symptoms are poorly understood. This gap in knowledge is in part due to the common confounds encountered in the study of the biology of psychotic symptoms, particularly the reality that the majority of psychotic patients are continuously treated with antipsychotic medications. One novel approach to investigating these questions, which circumvents this confound, is to explore the mechanisms of these symptoms in untreated individuals who are experiencing subsyndromal psychotic phenomena (i.e., below the clinical/disorder threshold). Recent evidence has suggested that such subthreshold psychotic symptoms are on a biological continuum with clinical psychosis (van Os J et al., 2009). Based on this "continuum" model of psychosis, in the current study, we characterized the subclinical delusional beliefs of a

cohort of young adults, testing whether specific, well-known types of delusional beliefs are associated with unique psychopathological correlates in this population.
Methods: Boston area college students underwent in-person assessments of psychopathology via a battery of self-report scales, which included a validated measure of subclinical delusions, the 21-item Peters et al Delusions Inventory (PDI) (Peters, E. R. et al., 1999). The items of the PDI are each comprised of a question (for example: "Do you ever feel as if the world is about to end?") to which the subject answers "yes" or "no". A prior factor analysis of data collected with the PDI (Peters, E. R. et al., 1999; Peters, E. R. et al., 2004) identified several independent clusters of items including a Persecutory Factor (PDI items 4 and 5: "Do you ever feel as if you are being persecuted in some way?", "Do you ever feel as there is a conspiracy against you?"), a Religiosity Factor (PDI items 8 and 11: "Do you ever feel that you are especially close to God?", "Do you ever feel as if you have been chosen by God in some way?"), and a Thought Disturbances Factor (PDI items 18 and 20: "Do your thought ever feel alien to you in some way?", "Do you ever feel as if your own thoughts were being echoed back to you?"). A logistic regression (n=702) was performed to ascertain whether the presence of certain symptoms or protective factors (including hallucinatory experiences, depressive symptoms, suicidality and resilience, measured using the Launay-Slade Hallucinations Scale (LSHS) (Waters F.A.V. et al., 2003), Beck Depression Inventory (BDI) (Beck, A.T. et al., 1996), Suicide Behaviors Questionnaire – Revised (SBQ-R) (Osman A. et al., 2001), and Connor-Davidson Resilience Scale (CD-RISC) (Connor K.M. and Davidson J.R.T., 2003, respectively) influenced the likelihood that participants endorsed one of these three clusters or types of delusional beliefs (as defined by the above three factors of the PDI): persecutory thinking, thought disturbances and religiosity.
Results: These analyses revealed that higher levels of depression symptoms were associated with an increased likelihood of experiencing persecutory thinking ($B = 0.072$; Wald = 15.14, $p < .001$, OR = 1.075). Also, higher levels of depression symptoms ($B = 0.038$; Wald = 5.13; $p = 0.023$; OR = 1.039) and hallucinatory experiences ($B = 0.080$; Wald = 55.29; $p < 0.001$; OR = 1.083) were associated with an increased likelihood of experiencing thought disturbances. Lastly, greater resilience ($B = 0.030$; Wald = 16.40; $p < 0.001$; OR = 1.031) was associated with an increased likelihood, whereas increased suicidality ($B = -0.094$; Wald = 3.991; $p=0.046$; OR = 0.910) was associated with a decreased likelihood, of religiosity.
Conclusion: Subclinical expressions of two types of delusional beliefs commonly observed in psychotic disorders, persecutory beliefs and "thought disturbances", were associated with depressive symptoms, similar to what has been observed in patients with psychotic illness (Smith B. et al., 2006). Moreover, thought disturbances, and to a lesser degree, religiosity, were linked to having hallucinatory experiences, further supporting the continuum model of psychosis. Lastly, religiosity was associated with higher levels of resilience and lower suicidality, indicating that some unusual, delusion-like beliefs may have protective features. Thus, this initial analysis of self-report data from a sample of non-help seeking young adults supports a model of delusions as a heterogeneous category of psychopathology.

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Mabel Toribio, M.D., Medicine - Endocrine-Neuroendocrine

Application of a Novel CD206+ Macrophage-Specific Arterial Imaging Strategy in HIV-infected Individuals

M. Toribio[1], M.V. Zanni[1], M.Q. Wilks[1], M.T. Lu[1], T.H. Burdo[2], J. Walker[3], P. Autissier[4], B. Foldyna[1], L. Stone[1], A. Martin[5], F. Cope[6], B. Abbruzzese[6], T. Brady[1], U. Hoffmann[1], K.C. Williams[4], G. El-Fakhri[1] and S.K. Grinspoon[1]

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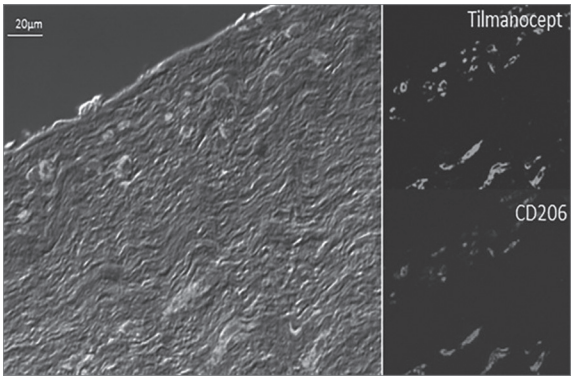
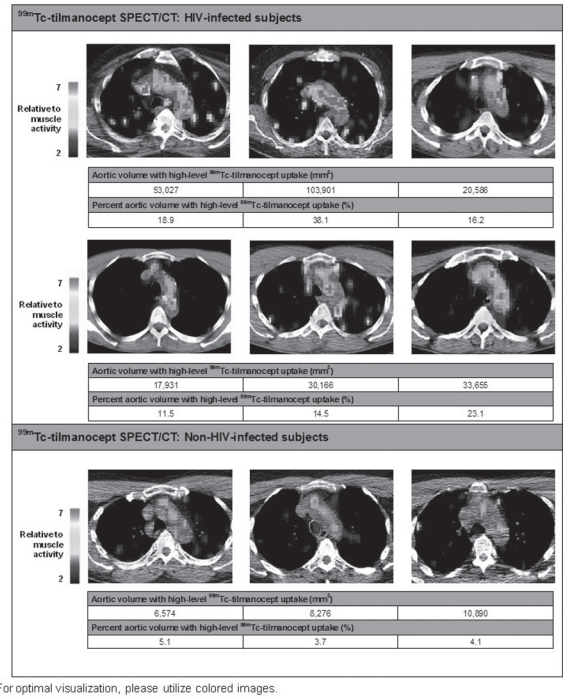
Introduction: Individuals living with HIV have an approximately 50% increased risk of atherosclerotic cardiovascular disease (CVD). This increased CVD risk is thought to be related to increased monocyte activation in HIV-infected individuals and levels markers of monocyte activation notably have been found to predict progression of atherosclerosis in HIV. Recent studies studying the role of different monocytes subsets in atherosclerosis, in particular, have demonstrated an increased density of CD206+macrophages in high-risk thin cap fiberoatheromas compared to stable thick cap fiberoatheromas. Evaluation of arterial CD206+ macrophage infiltration in HIV through a novel macrophage-specific imaging modality may improve our understanding of the pathophysiology of HIV-associated cardiovascular disease.
Methods: Co-localization of CD206+ and tilmanocept+ macrophages was evaluated by using double label immunofluorescence with a CD206 antibody and tilmanocept-Alexa-488 on tissue-banked aortic samples from HIV-infected individuals (N=10) and non-HIV-infected individuals (N=10). Technetium 99m tilmanocept (^{99m}Tc-tilmanocept) was then used for the first time in humans as a vascular imaging agent to evaluate macrophage-specific arterial infiltration in HIV-infected subjects (N=6) and non-HIV-infected subjects (N=3) using single-photon emission computed tomography/ computed tomography (SPECT/CT). Subjects were excluded if they had a prior history of cardiovascular disease or significant inflammatory disease or were taking systemic anti-inflammatory or immune suppressant medications. Comparisons between HIV-infected subjects and non-HIV-infected subjects were performed using a student's t-test for normally distributed variables and a Wilcoxon signed rank test for non-normally distributed variables.

Results: There was a high degree of co-localization of tilmanocept+ macrophages and CD206+ macrophages in aortic sections from HIV-infected (N=10) and non-HIV-infected individuals (N=10) (89.1 ± 6.3 % vs. 86.3 ± 6.8 %; Figure 1). Systemic administration of ^{99m}Tc-tilmanocept in humans resulted in markedly increased uptake in three sites: the liver, the kidney, and the aorta. The total aortic volume with high-level tilmanocept was higher in the HIV-infected group vs. the non-HIV-infected group ([31,910 (19,922, 65,745) vs. 8,276 (6,574, 10,890) mm^3], P=0.03). Among HIV-infected subjects with low Framingham risk scores, high-level ^{99m}Tc-tilmanocept uptake was present in 20.4% of the aortic surface volume versus 4.3% in non-HIV-infected control subjects (P=0.009; Figure 2). Among all subjects, noncalcified aortic plaque volume directly related to aortic high-level tilmanocept uptake (r = 0.87; P = 0.003), even after controlling for HIV status. Moreover, high-level tilmanocept uptake was also directly related to a marker of systemic monocyte activation, soluble CD14 (ρ=0.72, P=0.03).

Conclusion: There was a high degree of co-localization between C206+ and tilmanocept+ macrophages in aortic tissue samples from HIV-infected and non-HIV-infected individuals. In this first in human use of a CD206 macrophage-specific radiotracer as a vascular imaging agent, HIV-infected subjects demonstrated significantly greater high-level tilmanocept uptake along their aortic surface volume compared to non-HIV-infected subjects. The direct relationship between high-level tilmanocept uptake and noncalcified aortic plaque volume highlights a potential role for CD206+ macrophages in atherogenesis in HIV.



Tissue-banked aortic samples from individuals with and without HIV demonstrating co-localization of tilmanocept+macrophages and CD206+macrophages



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Aortic ^{99m}Tc-tilmanocept SPECT/CT in HIV-infected and non-HIV-infected subjects

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Bianca A. Trombetta, B.A., Neurology

Evaluating the use of a commercial ELISA for phenotyping Apolipoprotein E (ApoE) ε4 in cerebrospinal fluid and plasma

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Introduction: The Apolipoprotein E (*APOE*) gene is the major genetic risk factor for late-onset Alzheimer's disease (AD). Knowledge of *APOE* genotype status is often important for modeling experimental outcomes in studies using human tissue, but for a variety of reasons is not always available to researchers. Here, we examined whether expression of the ApoE ε4 isoform can be reliably used to infer *APOE* phenotype in human cerebrospinal fluid (CSF) and/or plasma. We examined the specificity of the assay for two binary classifications: 1) discerning between non-carriers and carriers of the ε4 allele, and 2) discerning between carriers of one and two copies of the ε4 allele.

Methods: We measured ApoE ε4 protein levels in 21 CSF samples and 18 plasma samples with known genotypes using a commercial ELISA specific to ApoE ε4. To determine the accuracy of the measure in discriminating between *APOE* genotypes, we classified samples by assigning phenotypes based solely on ApoE ε4 expression and defining reference ranges for each class. We then applied this measure to 116 CSF samples with unknown genotypes randomly selected from the Mass-General Institute for Neurodegenerative Disease (MIND) Tissue Bank, using designated classification criteria to determine *APOE* phenotypes. Confusion matrices in SPSS were used to determine specificity, and two-sample *t*-testing was used to examine differences in ApoE ε4 expression between classes. The range of protein expression for each class was calculated as 1.5 standard deviations beyond the mean of each group.
Results: The ApoE ε4 ELISA demonstrated 100% sensitivity and specificity for classifying non-carriers and carriers of the ε4 allele in both CSF and plasma samples for which carrier status was already determined through genetic testing. In discerning between one and two copies of the ε4 allele, the assay demonstrated specificity of 91.67% in CSF and 90.91% in plasma. Observed differences in ApoE ε4 expression between classes were significant within each binary classification ($p<0.001$) in both CSF and plasma. Using the reference ranges for each class, 96.55% (112/116) of the CSF samples examined were able to be classified as either non-carrier or carrier of the ε4 allele, and 92.24% (107/116) of the samples were able to be classified using all three phenotype distinctions, including differentiating between one and two copies of the ε4 allele. The observed distribution of *APOE* phenotypes in this cohort of CSF was comparable to reported prevalence of *APOE* genotype combinations (non-carrier: 55.17%, one copy of ε4: 18.97%, two copies of ε4: 14.66%).
Conclusion: Our findings provide preliminary evidence that it is feasible to use an ELISA specific to ApoE ε4 to identify *APOE* phenotype classifications from samples in which *APOE* carrier status is unknown. This assay has the potential to be of value to AD researchers, particularly in cases in which formal genetic testing is not available, by allowing this important variable to be accounted for in study analyses.

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Hoi See Tsao, M.D., Pediatrics

Limited English Proficiency Patient Education Access Initiative

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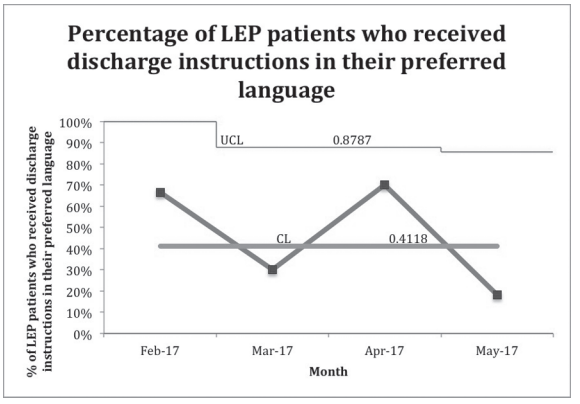
Introduction: Health disparities among patients with limited English proficiency (LEP) affect quality of care, length of stay, and readmission rates (Eneriz-Wiemer et al. 2014; Flores et al. 2005; Levas et al. 2011). A 2016 nursing and family needs assessment on the general pediatric inpatient floors at Massachusetts General Hospital indicated variability and potential disparities in the provision of discharge education materials to patients and families. Our aim is to provide standardized discharge patient education materials for an average of 60% of families who speak Spanish, Portuguese, or Arabic and who are discharged with one of the five most common medical diagnoses (asthma, bronchiolitis, pneumonia, seizures, and gastroenteritis) over the intervention measurement period.
Methods: On our inpatient pediatric units, 15% of families identified a preferred non-English language. The top three preferred non-English languages were Spanish (9.8%), Portuguese (1.7%) and Arabic (0.9%). We also analyzed admission data to identify the five most common medical diagnoses on the inpatient pediatric units: asthma, bronchiolitis, pneumonia, seizures and gastroenteritis. Diagnoses were assigned resident champions who reviewed available documents from commonly used sources. Using templates we developed for discharge instructions, resident champions created patient education handouts in English for each diagnosis. These handouts are currently being translated into Spanish, Portuguese, and Arabic. By September 2017, they will be available in our electronic health record's discharge module and we will have educated staff regarding their utilization. Starting in February 2017, we began a chart audit of patients discharged with any of the top five diagnoses to determine if discharge materials were provided in families' preferred language. All patients whose families were identified as Spanish-, Portuguese- or Arabic-speaking in this subset underwent chart review as well as a randomly selected sample of English-speaking patients. We created a Statistical Process Control (SPC) chart to track the percentage of patients for whom appropriate materials were provided. We will continue this audit after implementing the use of our new discharge handouts to determine whether we are successful in increasing the percentage of patients receiving materials in families' preferred languages. In addition, we have expanded our existing post-discharge follow-up telephone survey to ask families if they received patient education materials in their preferred language and for feedback on the materials. Modifications of the materials and workflow will be implemented based on the recommendations from post-discharge phone calls and staff feedback.
Results: Baseline performance via chart audit is in process. In February to May 2017, 18 to 70% of families received all discharge paperwork in their preferred non-English language. If we include families who received partially translated

discharge instructions, 50 to 90% of families received partial or all discharge paperwork in their preferred non-English language. We will assess post-implementation use of new materials in September to December 2017.
Conclusion: We have identified variability and potential disparities in currently used discharge education materials. We have created discharge handouts for the five most common diagnoses for which updated discharge materials would be most beneficial in English. The next steps will be to translate these documents into Spanish, Portuguese and Arabic, integrate them into the workflow, and educate staff regarding their availability, followed by data collection for outcome monitoring and implementation of feedback. Based on the lessons learned, this process can be expanded to other diagnoses, languages and departments such as the emergency department at our hospital, and other institutions. Citations: 1. Eneriz-Wiemer M et al, 2014. Parental Limited English Proficiency and Health Outcomes for Children with Special Health Care Needs: A systematic review. Academic Pediatrics 14(2): 128-136. 2. Flores G et al 2005. Limited English Proficiency, Primary Language at Home, and Disparities in Children's Health Care: How Language Barriers are Measured Matters. Public Health Reports 120: 418-430. 3. Levas MN et al, 2011. Effects of the Limited English Proficiency of Parents on Hospital Length of Stay and Home Health Care Referral for their Home Health Care-Eligible Children with Infections. Arch Pediatr Adolesc Med 165(9): 831-836.



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Miriam S. Udler, MD, PhD, Medicine - Endocrine-Diabetes

Key Biological Pathways Causing Type 2 Diabetes Determined By Cluster Analysis of Genetic Associations

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Introduction: Type 2 diabetes (T2D) is thought to be caused by multiple disparate biological pathways ultimately impacting glucose homeostasis. Over the past decade, close to 100 distinct genetic loci have been identified as associated with T2D through genomewide association studies (GWAS). Since these loci are predominantly in noncoding regions of the genome, the mechanisms by which they increase risk of T2D have not been fully elucidated. Therefore, to define key disease processes leading to T2D, we performed cluster analysis of variant-trait associations for the largest set of T2D genetic variants and diabetes-related traits to-date.
Methods: In the present analysis, 73 T2D genetic variants were selected as associated with T2D at genomewide significance from published GWAS. Summary statistic results of each variant's association with 31 diabetes-related traits were collated from published GWAS (e.g. BMI, fasting insulin, lipid values), and the variant-trait association strengths were represented as a 73-by-31 matrix of z-scores. We applied Bayesian Non-negative Matrix factorization to this matrix, producing clusters of variants and corresponding traits. This approach allows variants to be members of more than one cluster. We confirmed traits were associated with each cluster by performing a fixed-effect, inverse variance meta-analyses of variant-trait associations for each cluster.
Results: Our analysis yielded 4 robust clusters: (i) "Obesity" cluster of 3 variants defined by increased body mass index (BMI), waist circumference (WC), waist-hip ratio (WHR), leptin, and serum urate ($P<10^{-6}$); (ii) "Insulin Resistance" cluster of 24 variants defined by increased fasting insulin (FI), 2-hour post-challenge glucose, triglycerides, WHR, and decreased high density lipoprotein (HDL) cholesterol and birth weight ($P<10^{-5}$); "Beta-cell" cluster of 32 variants defined by increased fasting glucose, 2-hour glucose, and decreased BMI, WC, FI, and corrected insulin response ($P<10^{-6}$); and (iv) "Low Lipid" cluster of 5 variants defined by decreased low-density lipoprotein (LDL) and total cholesterol, triglycerides, urate, and gamma-linolenic acid ($P<10^{-5}$). In the "Low Lipid" cluster, 3 of the 5 variants have been associated with non-alcoholic fatty liver disease (NAFLD) at genome-wide significance. We then tested each cluster for aggregate variant risk of coronary artery

disease (CAD) and estimated glomerular filtration rate (eGFR) using published GWAS. The first 3 clusters were associated with increased risk of CAD (all $P<10^{-4}$), however, the "Low Lipid" cluster was not (P=0.9); this cluster was the only one associated with eGFR at $P<10^{-5}$, suggesting heterogeneity in the pathways impacting heart and kidney disease.
Conclusion: These results provide the most comprehensive delineation of common T2D genetic variants to-date, potentially highlighting distinct T2D subtypes with clinical implications.

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Michal Ursiny, MD, Urology

A Decision Analysis of Observation vs. Immediate Re-Intervention for Asymptomatic Residual Fragments < 4mm Following Ureteroscopic Lithotripsy

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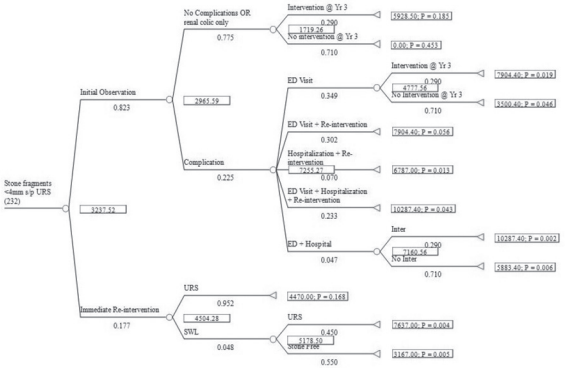
Introduction: Residual stone fragments 4mm or smaller after ureteroscopy have historically been considered to be clinically insignificant, but recent data has elucidated an approximately 20% stone event rate. Utilizing recent data from our recent study examining the natural history, complications, and re-intervention rates, we aimed to assess the cost-effectiveness of observation vs. intervention on asymptomatic residual fragments less than 4mm in diameter following ureteroscopic laser lithotripsy using a decision analysis model.
Methods: Outcomes data from a retrospective analysis evaluating the natural history, complications, and re-intervention rates of asymptomatic residual stone fragments performed by the EDGE consortium were utilized. A decision analysis model was constructed to compare the cost-effectiveness of initial observation of residual fragments compared to immediate intervention. Cost for the observation arm consisted of ED visits, hospitalizations, and re-interventions. The cost-analysis model extended for 3 years to account for delayed re-intervention rates on fragments of this size. For the immediate intervention arm, costs for ureteroscopy and shockwave lithotripsy were accounted and weighted depending on actual usage. Expected value calculations and sensitivity analyses were performed to determine the optimal treatment pathway based on overall cost-effectiveness inclusive of equipment, secondary costs from complications, emergency department visits, hospital readmission, and re-interventions. Costs of emergency department visits, readmissions, and re-interventions were calculated based on published figures from the literature.
Results: Two hundred thirty-two patients were found to have asymptomatic residual fragments < 4mm on follow-up imaging following ureteroscopic lithotripsy. There were 191 patients in the observation group and 41 in the immediate-intervention group. Decision analysis modeling demonstrated that when comparing initial observation to immediate re-intervention, the cost was $2965 vs. $4504, respectively. The difference in cost was largely driven by the fact that over 3 years, approximately 56% of patients remain asymptomatic and thus incur no ED visit, hospitalization, or re-intervention costs. This represents an approximate annual per-patient savings of $513, and $1539 over three years when observation is selected over immediate re-intervention.
Conclusion: Our decision analysis model demonstrates superior cost-effectiveness for observation over immediate re-intervention for asymptomatic residual stones < 4mm following ureteroscopic lithotripsy. The cost-savings are primarily due to a plurality of patients not requiring intervention if observed. Based on these findings, careful stratification and selection of patients may enable surgeons to improve cost-effectiveness of managing small, asymptomatic residual fragments following ureteroscopic lithotripsy.



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Jonathan Van Ornam, Emergency

The Utility of Repeat Routine Computerized Tomography Scans in Patients With Mild Traumatic Intracranial Hemorrhage

J. Van Ornam[1], P. Pruitt[2] and P. Borczuk[1]

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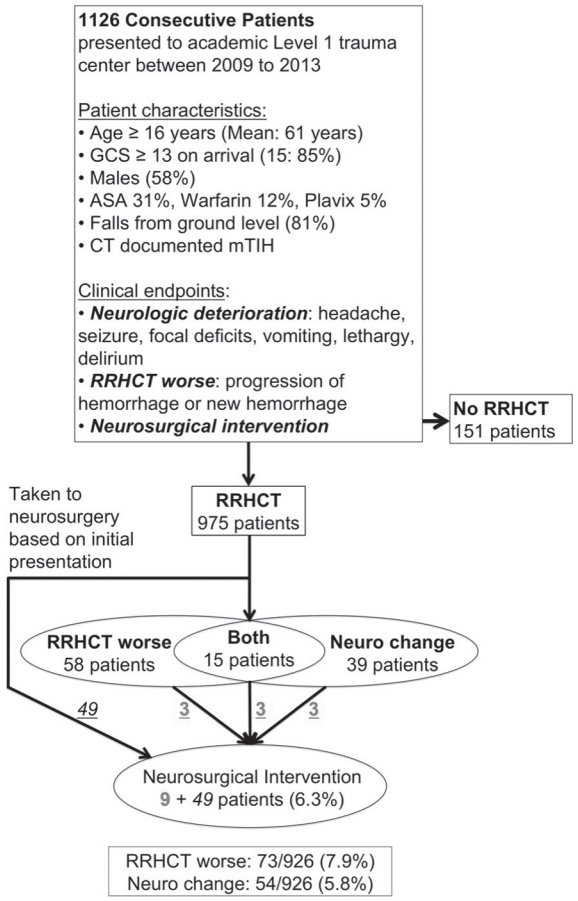
Introduction: Patients with mild traumatic intracranial hemorrhage (mTIH), defined as hemorrhage with Glasgow Coma Scale (GCS) ≥ 13 frequently receive routine repeat head CT scans (RRHCT) to assess for progression of hemorrhage regardless of clinical status.
Methods: Retrospective review of 1126 consecutive patients age ≥ 16 with CT-documented mTIH and GCS ≥ 13 who presented to an urban, university affiliated, 100,000 annual visit ED between 2009-2013. Data elements include demographics, the number of imaging studies performed during admission and three clinical endpoints including neurologic deterioration, hemorrhage progression on repeat CT scan, and the need for neurosurgical intervention.
Results: 975 patients (86.6%) had RRHCT. Mean age was 60.6 (range 16-101) years and 58% of subjects were male. Ground level falls caused injury in 81% of patients. 11.8% used warfarin daily, while 4.8% used clopidogrel daily. 84.8% had an initial GCS of 15. While in the ED or as an inpatient, 54 patients (5.6%) had neurologic deterioration, 73 (7.5%) had hemorrhage progression on repeat CT scans, and 58 (5.9%) required neurosurgical intervention. 49 patients (5%) underwent neurosurgical intervention without either neurologic deterioration or hemorrhage progression on RRHCT. Notably, only 3 patients (0.3%) underwent neurosurgical intervention after hemorrhage progression on repeat CT scan in the absence of neurologic deterioration. All 3 of these patients had initial subdural hematomas > 1 cm with subsequent expansion and only one of these patients had a GCS of 15. There were 1840 CTs performed for the 683 patients with an initial GCS of 15 who had none of the three clinical endpoints (2.7 CT scans/patient).
Conclusion: RRHCT in patients with mTIH appears to have little impact on clinical management. In these patients, about 305 repeat CT scans would be needed to identify one patient who subsequently undergoes neurosurgical intervention. A more effective alternative approach may be to clinically monitor for neurologic deterioration without additional imaging. Future research should be directed at comparing these two approaches in terms of utility and cost and classifying potential high risk subgroups of mTIH for which RRHCT is appropriate.



Clinical Endpoints Correlate with Initial Glasgow Coma Scale				
Initial GCS	Total	RRHCT worse	Neurologic deterioration	Neurosurgery intervention
15	807	52 (**6%**)	35 (**4%**)	43 (**5%**)
14	118	10 (**8%**)	9 (**8%**)	10 (**8%**)
13	50	11 (22%)	10 (20%)	5 (10%)

Patient characteristics with resulting outcomes.

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Carrie Vaudreuil, MD, Psychiatry

Is Subthreshold Pediatric Bipolar Disorder Morbid? A Systematic Literature Review and Meta-Analysis

C. Vaudreuil[1], S. Faraone[2], J. Wozniak[1], N. Carrellas[1] and J. Biederman[1]

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Introduction: Because pediatric bipolar-I (BP-I) disorder tends to evolve over time, some youth present to clinical attention with insufficient symptoms to fulfill full diagnostic threshold for a diagnosis of BP-I disorder. However, while much is known about full threshold BP-I disorder, little is known about subthreshold forms of pediatric BP-I disorder (SubBP-I). The importance of subthreshold psychiatric diagnoses has been widely recognized in adult psychiatry. A survey of 2406 adults followed up for 18 months documented that subthreshold adult psychiatric symptoms predicted functional disability at follow up. The authors of this study concluded that "the importance of subthreshold symptoms should not be underestimated" (Raj et al, 2010). Others authors have argued that a 'mood spectrum model' is important in identifying individuals with severe psychopathology not adequately attended to in the DSM 5 (Benvenuti et al, 2015). Yet, uncertainties remain as to whether SubBP-I in children is a meaningful clinical entity. Whether SubBP-I disorder represent a meaningful clinical entity associated with morbidity and dysfunction has important clinical, scientific and public health relevance. If pediatric SubBP-I disorder is found to be morbid, clinicians should consider identifying and treating such patients. Such interventions can mitigate the progression of the disorder to a full syndromatic state. Scientifically, such information can allow the identification of neurobiological precursors to pediatric BP-I disorder before the confounders of chronicity and treatment makes interpretation of findings difficult. From the public health perspective, this information can lead to the improved efforts aimed at screening children at risk for BP-I disorder in the primary care setting and the development of early intervention strategies aimed at mitigating the progression of the disorder to its fullest morbidity. The main aim of the present study was to examine what is known about pediatric SubBP-I. To this end we conducted a systematic review the extant literature on the

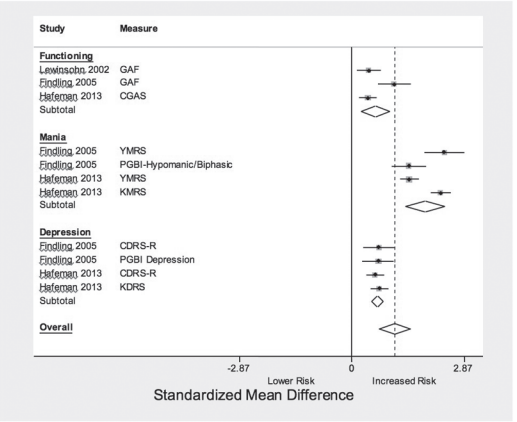
subject and subjected the data to a qualitative analysis and meta-analysis. We hypothesized that pediatric SubBP-I disorder would be prevalent and morbid. To the best of our knowledge, this represents the first systematic review of the literature and meta-analysis on pediatric SubBP-I.

Methods: Study Selection: Thirty seven full text articles were reviewed and 11 papers, consisting of 7 datasets, were included in the meta-analysis. Data Extraction: The following variables were extracted: study sample, mean age of probands, the percentage of male probands, the source of probands (community or clinic), type of controls (psychiatric versus non mentally ill), length of follow up in years (for longitudinal studies), and outcomes related to subthreshold BP-I morbidity, including assessment of functioning, severity of mood symptoms, psychiatric comorbidities, suicidal ideation and associated behaviors, and utilization of mental health services. Statistical Analysis: We used meta-analysis to compute the pooled standardized mean difference (SMD) between two pairs of groups: subjects with subthreshold pediatric BP-I vs. non-Bipolar controls, and subjects with subthreshold pediatric BP-I disorder vs. those with full threshold pediatric BP-I disorder.

Results: Subthreshold pediatric BP-I was associated with greater functional impairment, greater severity of mood symptomatology, higher rates of disruptive behavior, mood and substance use disorders, and higher rates of suicidal ideation and attempts when compared to non-bipolar controls. There were no differences between full and subthreshold cases in the severity of depressive symptoms, rates of other comorbid disorders, rates of suicidal ideation and attempts, and rate of mental health treatment utilization.

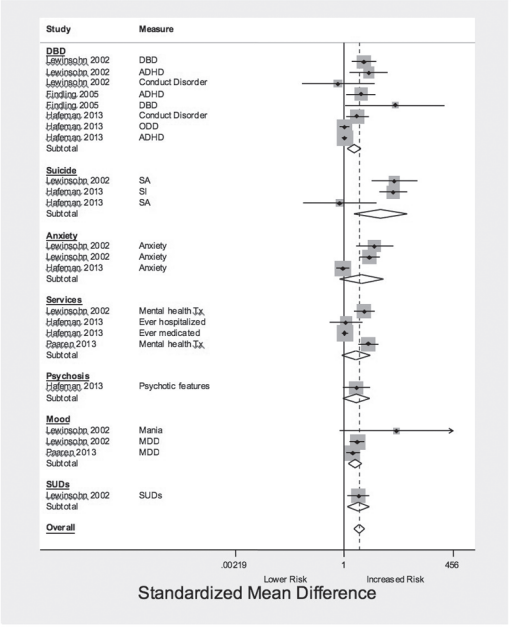
Conclusion: Subthreshold pediatric BP-I disorder is an identifiable morbid condition associated with significant functional impairment including psychiatric comorbidities and high rates of suicidality.

Figure 1: Comparison of level of functioning and severity of mood symptoms in youth with SubBP vs Controls.



GAF = Global Assessment of Functioning; CGAS = Children's Global Assessment Scale; YMRS = Young Mania Rating Scale; PGBI = Parent General Behavior Inventory; KMRS = Kiddie Schedule for Affective Disorders (KSADS) Mania Rating Scale; CDRS-R = Children's Depression Rating Scale-Revised; KDRS = KSADS Depression Rating Scale.

Figure 2: Comparison of comorbid psychiatric disorders, suicidality, and utilization of mental health services in SubBP vs Controls.



DBD = Disruptive behavior disorders; ADHD = Attention deficit hyperactivity disorder; ODD = Oppositional defiant disorder; SA = Suicide attempts; SI = Suicidal ideation; Tx = Treatment; MDD = Major depressive disorder; SUDs = Substance use disorders

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Julian A. Villalba, MD, Pathology

High frequency of false-positive results of lupus anticoagulant tests in patients receiving argatroban

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Introduction: Argatroban is a direct, selective thrombin inhibitor. The U.S. Food and Drug Administration licensed its use for prophylaxis or treatment of thrombosis in heparin-induced thrombocytopenia (HIT) patients or in patients undergoing percutaneous coronary intervention with or at risk for HIT. Patients receiving argatroban frequently undergo lupus anticoagulant testing because they often have had a thrombotic event or suspected hypercoagulability. Lupus anticoagulants cause hypercoagulability and thrombosis. Thus, we sought to determine if argatroban can interfere with lupus anticoagulant (LA) testing.

Methods: To evaluate the effect of argatroban on LA testing, we prospectively assessed LA testing for consecutive patients when they were receiving argatroban and compared the results with when they were not receiving argatroban to determine the interference of argatroban on these assays. LA testing included the lupus anticoagulant-sensitive activated partial thromboplastin time (PTT-LA) assay, 1:1 mixing, and the confirmatory hexagonal phase (Staclot-LA) assay. We determined the rate of false-positive and false-negative results of LA tests on ex vivo specimens from patients treated with argatroban.
Results: Over a 2.5 year period, 48 patients receiving argatroban were identified from the total pool of patients undergoing lupus anticoagulant testing (n=15,526). Once a patient was determined to be receiving argatroban, an additional plasma specimen before starting argatroban therapy or after discontinuation of argatroban therapy was retrieved. For plasma specimens collected after argatroban was discontinued, a thrombin time was performed and was demonstrated to be normal to ensure that argatroban was no longer present. A total of 101 samples from 37 patients with or without argatroban were available for LA testing. All patients had a prolonged activated partial thromboplastin time (aPTT) when they were receiving argatroban (mean ± SD: 65.2 ± 23.6 seconds). All argatroban specimens but one showed significant prolongations in the PTT-LA (mean ± SD: 88 ± 32.4 seconds; $p \leq 0.0001$)(**Fig. 1A**). LA testing was confirmed true-positive in 38% (14/37) of samples from patients when not receiving argatroban. Among them, 100% were also positive when on argatroban (mean Staclot LA delta ± SD: off argatroban 16.9 ± 9.6 seconds, on argatroban 30.4 ± 15.4 seconds, where positive is >8 seconds; $p \leq 0.0001$)(**Fig. 1B**). For patients without LA at baseline, the mean PTT-LA significantly increased when on argatroban (mean ± SD: off argatroban 41.6 ± 12 seconds, on argatroban 87.6 ± 32.1; $p \leq 0.0001$)(**Fig. 1C**). Among them, all but one (22/23) became false-positive when on argatroban (mean delta ± SD: off argatroban 3 ± 2.5 seconds, on argatroban 25.8 ± 17.7 seconds, where positive is >8 seconds; $p \leq 0.0001$)(**Fig. 1D**), leading to a 95.7% false positive rate in confirmatory testing. These effects were seen even in specimens containing low subtherapeutic argatroban levels. Argatroban did not cause any false-negative results. Both PTT-LA (**Fig. 2A**) and the confirmatory hexagonal phase (Staclot-LA) assay (**Fig. 2B**) were positively correlated with aPTT when tested on argatroban specimens, suggesting a dose-dependance effect of the drug in both tests.
Conclusion: Argatroban significantly affects LA testing. The rate of false-positive results in LA testing is unacceptably high in patients receiving argatroban. Clinicians should be advised that LA testing for patients receiving argatroban is not accurate.

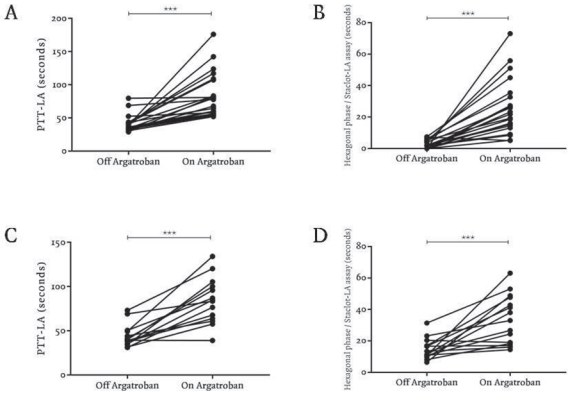

Fig 1. Lupus anticoagulant-sensitive activated partial thromboplastin time (aPTT-LA) and the confirmatory hexagonal phase (Staclot-LA) assay for patiens without lupus coagulant at baseline (**A and B**) vs. patients with lupus anticoagulant at baseline (**C and D**).

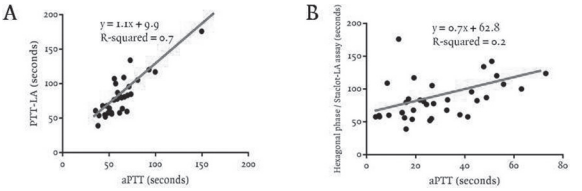

Fig 2. Scatter plot of the total data showing an overall positive correlation of the anticoagulant-sensitive activated partial thromboplastin time (aPTT-LA) (**A**) (Two-tailed Pearson's correlation, $p \leq 0.001$), and the confirmatory hexagonal phase (Staclot-LA) assay (**B**) (Two-tailed Pearson's correlation, p=0.009) with the activated partial thromboplastin time (aPTT) when tested on specimens containing argatroban.

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Ana C. Villegas, M.D., Athinoula A. Martinos Center for Biomedical Imaging

TMS treatment of refractory Major Depressive Disorder with comorbid Alzheimer's Mild Cognitive Impairment: a case report

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Introduction: Major depressive disorder (MDD) presents with cognitive deficits which, in geriatric populations, may be confused with a neurodegenerative dementia. Repetitive Transcranial Magnetic Stimulation (rTMS) is an established noninvasive neuromodulation technique FDA cleared for the treatment of MDD. Recent evidence has suggested the potential therapeutic role of TMS in delaying cognitive decline from neurodegenerative dementias.
Methods: We describe a case of a 66 year old female with MDD and Alzheimer's mild cognitive impairment (MCI) who received a course of TMS treatment for MDD.

Results: The intervention led to remission of her depressive symptoms (HAMD17 = 6). Her memory impairment and decline, however, remained essentially unchanged as measured by the Montreal Cognitive Assessment (MoCA) and psychiatric and neurological evaluation. TMS was well tolerated and did not lead to side effects.
Conclusion: This case suggests that TMS is a safe and effective treatment for MDD in the context of a neurodegenerative disorder. The standard antidepressant protocol did not lead to improvement in cognition: we propose mechanistic hypotheses for this dissociation. rTMS may be useful to differentiate between reversible and neurodegenerative causes of cognitive decline, as well as an early therapeutic intervention.

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Christine Vogeli, PhD, Medicine - Mongan Institute for Health Policy

Utilization patterns and care management needs of Medicaid beneficiaries

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Introduction: Many health systems, including Partners, have implemented care management programs to mitigate cost and utilization for high-risk patients who typically have multiple chronic conditions or complex psychosocial needs. As Partners pursues accountable care in the Medicaid population, it is important to investigate the ways in which high-risk Medicaid patients engage with the health care system. Past studies have found that Medicaid patients often encounter barriers to accessing primary care and therefore, have particularly high emergency department (ED) utilization.[1] However, because these patients are frequently younger and less medically complex, they may be overlooked for care management. Our analysis aims to observe differences in utilization, costs, social needs, and access to care between Medicaid patients engaged in the Partners Integrated Care Management Program (iCMP) and non-iCMP Medicaid patients with high ED utilization. [1] Taubman S, Allen H, Wright B, Baicker K, Finkelstein A. Medicaid Increases Emergency Department Use: Evidence from Oregon's Health Insurance Experiment. *Science.* 2014; 343:263-268.
Methods: This cross-sectional study utilizes claims data from iCMP and non-iCMP Medicaid patients enrolled in a managed care plan. To be included in the analysis, patients had to be 18 years or older and enrolled in the Medicaid plan for at least 6 months from September 2015 through August 2016. iCMP Medicaid patients and a comparison of non-iCMP Medicaid patients with three or more ED visits from September 2015 through August 2016 were surveyed by phone between December 2016 and January 2017. The analysis compares the characteristics of all iCMP and non-iCMP Medicaid patients, as well as characteristics within the high ED utilization subset.
Results: We identified 26,856 Medicaid patients who met the inclusion criteria. Of these patients, 1,291 (4.8%) had three or more ED visits from September 2015-August 2016. 5.1% of those with high ED utilization were enrolled in iCMP, comprising 15.2% of the overall iCMP Medicaid population (n=435). Patients engaged in iCMP were significantly older and had more chronic conditions than those not engaged in the program. Regardless of risk score, iCMP and non-iCMP patients with high ED utilization presented at the ED for similar reasons. Common primary diagnoses included behavioral health conditions, unspecified pain, and conditions treatable in a primary care setting. The iCMP patients with high ED use had higher annual rates of hospitalizations (1.37 compared to 0.25 in the non-iCMP group), primary care visits (4.78 compared to 2.78), and specialist visits (7.66 compared to 4.07). Although the iCMP patients with high ED utilization had significantly higher annual total medical expense (TME) than the non-iCMP group ($41,848 compared to $16,380), the non-iCMP group's TME exceeded that of iCMP patients with low ED utilization ($14,530). Despite age and health status, there was no significant difference in iCMP and non-iCMP patients' self-rated health or level of concern for their health. They also had similar levels of concern about health-related social needs, such as transportation to appointments, housing stability, food security, etc. Non-iCMP patients were more likely to report delaying care because of appointment availability and clinic hours compared to iCMP patients.
Conclusion: This study suggests that despite being engaged in care management, a segment of the Medicaid population is frequently using the ED for behavioral health or primary care treatable conditions. The non-iCMP patients are not typically thought to be high-risk, as they are younger with fewer chronic conditions and lower overall utilization. However, this analysis suggests that they have similar costs to patients receiving care management and may be experiencing more barriers to accessing care. To expand on this work, we plan to examine the stability of care management needs over time in this population. Future research is needed to determine if care management is the most appropriate and effective strategy for reducing preventable ED visits among Medicaid beneficiaries with high ED use. As Partners transitions to Medicaid accountable care, this subset of patients may represent an opportunity to improve engagement with primary care and reduce costs.

Table 1. Characteristics of iCMP and non-iCMP Medicaid patients by ED utilization

	iCMP Medicaid		non-iCMP Medicaid	
	0 ED visits	3 or more ED visits	3 or more ED visits	p-value
	n=227	n=66	n=1225	
% Female	60.4%	68.2%	66.5%	0.18
Age				
18-21 years	1.8%	1.5%	8.5%	<0.0001
22-34 years	10.1%	27.3%	42.2%	
35-44 years	17.2%	19.7%	22.7%	
45-54 years	32.2%	24.2%	16.9%	
55-64 years	38.8%	27.3%	12.2%	
Average Impact Pro Risk Score	5.21	8.43	3.52	<0.0001
% identified as high-risk	27.0%	66.7%	32.1%	<0.0001
Average # of low risk conditions	0.75	0.8	0.55	0.0003
Average # of moderate risk conditions	0.47	0.97	0.39	<0.0001
Average # of high risk conditions	0.51	0.67	0.2	<0.0001

Table 2. Annual rates of utilization and costs in iCMP and non-iCMP Medicaid patients

	iCMP Medicaid		non-iCMP Medicaid
	0 ED visits	3 or more ED visits	3 or more ED visits
	n=227	n=66	n=1225
ED visits	0	5.7	4.7
Hospitalizations (Medical)	0.25	1.37	0.25
Primary Care Visits	3.16	4.78	2.78
Specialist Visits (including behavioral health)	5.65	7.66	4.07
Total Medical Expense (TME)	$14,530	$41,849	$16,381

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Christine Vogeli, PhD, Medicine - Mongan Institute for Health Policy

Comparison of integrated care management program patients selected from an administrative claims-based algorithm and patients opted in by primary care physicians

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Introduction: The integrated care management program (iCMP) is a primary care based program that provides additional support to chronically ill, medically-complex patients. Primary care providers work with their iCMP care team to select patients for the program. Patients are either selected from a list generated by an administrative claims-based algorithm, or can be opted in to the program. The majority of iCMP patients are selected from the list generated by the algorithm; however, a growing proportion of patients are opted in to the program. The objective of this analysis was to determine if there are differences in demographics and health-related social needs between algorithm-identified and opt-in patients. In addition, we compared health care utilization during the 12 months before and 12 months after iCMP enrollment between these patient groups.

Methods: iCMP patients enrolled between January 2015 and March 2016 were eligible for this analysis. We excluded patients who were not aligned to Partners Healthcare for at least 10 months before and after their iCMP enrollment date. Bivariate analyses were used to detect differences in demographics, drug and alcohol use, housing and economic instability, and physical or sexual abuse prior to iCMP enrollment. Repeated measures ANOVA was used to detect difference-in-differences for ED visits and hospitalizations before and after iCMP enrollment.

Results: There were 2,327 eligible patients enrolled in iCMP between January 2015 and March 2016 and 404 (17%) were opted in to the program by their PCP. The average age of the patients was 71 years, two-thirds (60%) were female, and the majority (90%) were white. Significantly more opt-in patients had an academic medical center (AMC) based PCP (51% vs. 40% of algorithm-identified, $p<0.0001$). There were no differences in drug and alcohol use or housing and economic instability between opt-in and algorithm-identified patients. However, opt-in patients may have experienced more physical or sexual abuse than algorithm-identified patients (1.2% vs. 0.4%, $p=0.04$). Significantly fewer opt-in patients had at least one ED visit or at least one hospitalization before iCMP enrollment than algorithm-identified patients (ED visits: 35% vs. 41%, $p=0.04$; hospitalizations: 32% vs. 40%, $p<0.01$). After adjustment for practice location (AMC vs. non-AMC), medical and surgical hospitalizations during the 12 months after iCMP enrollment declined significantly for both patient groups (medical $p=0.03$; surgical $p<0.01$).

Conclusion: Despite less health care utilization prior to iCMP, opt-in patients experienced similar declines in utilization after enrollment. The larger proportion of opt-in patients from AMC-based PCPs may be due to differences in care team composition, such as the addition of community health workers at AMC practices. Opt-in patients were more likely to experience abuse but may also have had more health-related social needs that we were not able to assess. The administrative claims-based algorithm is currently being revised to include more clinical and psychosocial information in order to better identify persons who could benefit from iCMP. Improved identification and documentation of health-related social needs may also enhance the ability to identify patients who would benefit from the program.

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Sarah E. Wakeman, Medicine

Inpatient Addiction Consultation for Hospitalized Patients Increases Post-Discharge Abstinence and Reduces Addiction Severity

S.E. Wakeman[1,2,3], J. Metlay[2,3], Y. Chang[4], G.E. Herman[1] and N. Rigotti[2,3]

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Introduction: Alcohol and drug use results in substantial morbidity, mortality, and cost. Individuals with alcohol and drug use disorders are overrepresented in general medical settings. Hospital-based interventions offer an opportunity to engage with a vulnerable population that may not otherwise seek treatment.

Methods: Researchers designed a prospective, quasi-experimental evaluation comparing 30-day post-discharge outcomes of participants who were or were not seen by an addiction consult team during hospitalization at Massachusetts General Hospital. The study sample was comprised of 399 hospitalized adults who screened high risk for having an alcohol or drug use disorder or who were clinically identified by the primary nurse as having a substance use disorder. The intervention was an addiction consultation from a multidisciplinary specialty team offering pharmacotherapy initiation, motivational counseling, treatment planning, and direct linkage into ongoing addiction treatment. The main measures of the study were Addiction Severity Index (ASI) composite score for alcohol and drug use and self-reported abstinence at 30-days post-discharge. Secondary outcomes included 90-day substance use measures and self-reported hospital and ED utilization.

Results: Among 265 participants with 30-day follow-up, the ASI composite score for drug or alcohol decreased more in the intervention group compared to the control group (mean ASI-alcohol decreased by 0.24 vs. 0.08, p<0.001; mean ASI-drug decreased by 0.05 vs. 0.02, p=0.003.) Days abstinent increased more in the intervention group versus the control group (+12.7 days versus +5.6, p<0.001). The differences in ASI-alcohol, ASI-drug and days abstinent all remained statistically significant after controlling for age, gender, employment status, smoking status, and baseline addiction severity (p=0.018, 0.018, and 0.02, respectively). In a sensitivity analysis assuming that patients who lost to follow-up had no change from baseline severity, the differences remained statistically significant.

Conclusion: In a non-randomized cohort of medical inpatients, addiction consultation reduced addiction severity for alcohol and drug use and increased the number of days abstinent in the first month after hospital discharge.

Baseline characteristics of all enrolled patients

	All (N=399)	Intervention (N=256)	Control (N=143)	P value
Major substance problem, N (%)				0.88
Alcohol	218 (55)	141 (55)	77 (54)	
Drug	143 (36)	92 (36)	51 (36)	
Both	38 (10)	23 (9)	15 (10)	
Age, Mean (SD)	48 (14)	46 (13)	51 (15)	0.006
Female, N (%)	110 (28)	77 (30)	33 (23)	0.14
Caucasian, N (%)	324 (81)	209 (82)	115 (80)	0.76
Education, N (%)				0.88
High school or less	216 (54)	142 (55)	74 (52)	
More than high school	91 (23)	59 (23)	32 (22)	
Unknown	92 (23)	55 (21)	37 (26)	
Employment Status, N (%)				<0.001
Employed/Student	81 (20)	42 (16)	39 (27)	
Retired	32 (8)	11 (4)	21 (15)	
Disabled	78 (20)	49 (19)	29 (20)	
Not employed	179 (45)	135 (53)	44 (31)	
Unknown	29 (7)	19 (7)	10 (7)	
Smoking Status, N (%)				0.002
Never	53 (13)	31 (12)	22 (15)	
Past	37 (9)	14 (5)	23 (16)	
Active	255 (64)	177 (69)	78 (55)	
Unknown	54 (14)	34 (13)	20 (14)	
Baseline ASI alcohol, Mean (SD)	0.41 (0.33)	0.46 (0.34)	0.31 (0.31)	<0.001
Baseline ASI drug, Mean (SD)	0.13 (0.15)	0.15 (0.16)	0.10 (0.11)	<0.001

Substance Use Outcomes

		30-day follow-up			90-day follow-up		
		Intervention (N=165)	Control (N=100)	P value	Intervention (N=144)	Control (N=83)	P value
ASI alcohol	Baseline	0.46 (0.33)	0.28 (0.29)	<0.001	0.47 (.32)	0.30 (0.31)	<0.001
	Follow-up	0.22 (0.22)	0.20 (0.20)	0.45	0.25 (0.22)	0.20 (0.22)	0.12
	Change	-0.24 (0.28)	-0.08 (0.24)	<0.001	-0.22 (0.29)	-0.10 (0.27)	0.003
	Adjusted Difference*	-0.06 (0.02)		0.018	-0.01 (0.03)		0.79
ASI drug	Baseline	0.13 (0.16)	0.10 (0.11)	0.057	0.12 (0.15)	0.09 (0.11)	0.17
	Follow-up	0.08 (0.11)	0.08 (0.09)	0.74	0.07 (0.08)	0.07 (0.08)	0.89
	Change	-0.05 (0.11)	-0.02 (0.08)	0.003	-0.05 (0.11)	-0.02 (0.09)	0.058
	Adjusted Difference*	-0.02 (0.01)		0.018	-0.01 (0.01)		0.12
Days abstinent	Baseline	12.6 (10.6)	19.1 (11.1)	<0.001	13.2 (11.0)	18.6 (11.2)	<0.001
	Follow-up	25.3 (8.3)	24.7 (7.9)	0.57	24.3 (9.3)	24.1 (9.9)	0.88
	Change	12.7 (11.7)	5.6 (10.2)	<0.001	11.0 (12.7)	5.5 (10.5)	<0.001
	Adjusted Difference*	2.59 (1.11)		0.02	1.70 (1.35)		0.21
Overdose	Baseline	0.23 (0.85)	0.23 (0.96)	0.99	0.24 (0.89)	0.17 (0.60)	0.5
	Follow-up	0.04 (0.30)	0.06 (0.24)	0.60	0.01 (0.08)	0.04 (0.33)	0.43
	Change	-0.19 (0.73)	-0.17 (0.85)	0.86	-0.23 (0.90)	-0.13 (0.44)	0.28
	Adjusted Difference*	-0.03 (0.03)		0.42	0.01 (0.01)		0.48

** The difference in changes from baseline to follow-up between intervention and control group from regression models adjusting for age, gender, employment status, smoking status, and baseline value*

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Rochelle Walensky, Medicine - General Internal Medicine

The Clinical and Economic Impact of Attaining National HIV/AIDS Strategy Treatment Targets in the US

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Introduction: The US National HIV/AIDS Strategy (NHAS) aims for 72% (90% diagnosed x 80% of those virally suppressed) viral suppression among people with HIV by 2020. We examined the clinical and economic impact of reaching this target, in the general population (US) and among black men who have sex with men (black MSM), the group with the highest HIV prevalence.
Methods: Using a mathematical simulation, we project the 5- and 20-year clinical outcomes, costs, and incremental cost-effectiveness ratios (ICERs) for: 1) *Current Pace* of detection, linkage, retention, and virologic suppression; and 2) *NHAS* investments in expanded testing ($24-74/test) and adherence ($400/person/year), calibrated to achieve 72% suppression by 2020. We examined alternative rates of testing, retention, and suppression and the efficacy and cost of adherence interventions.
Results: Compared to *Current Pace* over 20 years *NHAS* averted 280,000 (black MSM:80,000) HIV transmissions, 199,000 (black MSM:45,000) deaths and saved 2,138,000 (black MSM:453,000) years of life, while increasing costs by 23%. The ICER for *NHAS* compared to *Current Pace* was $68,900/quality-adjusted life-year (QALY; black MSM:$38,300/QALY) and was most sensitive to antiretroviral therapy costs.
Conclusion: Reaching *NHAS* targets would yield substantial clinical benefits and be cost-effective in both the general US and black MSM populations.

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Rachel Wallwork, MD, Medicine

Rituximab for Idiopathic and IgG4-Related Retroperitoneal Fibrosis

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Introduction: Untreated retroperitoneal fibrosis (RPF) can lead to chronic back and flank pain and/or renal failure. The mainstay of treatment for non-malignant (IgG4-related disease [RD] or idiopathic) RPF is glucocorticoid (GC) therapy which often has insufficient efficacy or is complicated by toxicity. We performed a retrospective review of patients with RPF treated with rituximab (RTX).
Methods: We reviewed the database of the Massachusetts General Hospital's Center for IgG4-RD and identified all RPF patients with RPF treated with RTX who had follow-up (2010-2016). RPF was diagnosed by CT or MRI following commonly accepted radiological criteria (*Lancet* 2011;378:338). Demographics, date of symptom onset and diagnosis, symptoms, co-morbidities, laboratory values, use of stents or percutaneous nephrostomy (PCN) tubes, biopsy results, and symptomatic response to treatment were collected from the database. A board-certified radiologist (AS) reviewed baseline and follow-up imaging. Response to treatment was defined (*Lancet* 2011;378:338) as symptom improvement or radiographic improvement (reduction in lesion size in at least two radiographic planes).
Results: Twenty-six RPF patients received RTX (**Table 1**). The median age was 55 years (IQR 43, 58) and a majority wasere male (85%) and former or current smokers (85%). Pathology was availableThe lesion was biopsied in 20 (77%) patients. In 17/20 (85%) patients, diagnostic features of IgG4-RD were present; in the remaining and in 3/20 (15%) malignancy and infection were ruled out but specific features of IgG4-RD were absent. Of the six patients not biopsied, 2 (33%) met clinical diagnostic criteria for IgG4-RD and four had typical radiographic idiopathic RPF with no clinical suspicion of infection or malignancy. Ten of 26 (39%) patients had previously failed GC therapy. RTX was used as monotherapy in 20 (77%) patients and in combination with GC in 6 patients (23%); ten (39%) patients required ureteral stents or PCN tubes. Of the 21 patients with baseline symptoms (e.g., pain), all (100%) had improvement. Twenty-two (88%) of the 25 patients with follow-up imaging had radiographic improvement (reduction in lesion size in at least two radiographic planes); in the remaining 3 patients, the RPF remained stable. Of the 10 patients with a stent or PCN, 4 (40%) had it successfully removed. Four of the six patients whose stents or PCN were not removed had disease duration for greater than 1 year prior to RTX.

Conclusion: In this retrospective study of patients with idiopathic or IgG4-related RPF, peripheral B cell depletion with RTX was highly effective. It, was used as monotherapy in the majority of patients. A striking proportion (85%) were current or former smokers. Future research could explore whether pPatients with disease for greater than 1 year prior to RTX may responded less well.

Table 1: Baseline Demographics and Features with Treatment Response

Sample Size	26
Age at Diagnosis (Median, IQR)	55 (43, 58)
Male (%)	22 (85%)
Non-Hispanic White	19 (73%)
Smoking History	22 (85%)
Former	16 (62%)
Current	6 (23%)
Serum IgG4 Concentration Elevated	11 (42%)
Other Organ Involvement	6 (23%)
Diagnostics	
Typical Radiographic Appearance	26 (100%)
RPF Biopsied	20 (77%)
Diagnostic of IgG4-RD	17 (65%)
Suggestive of IgG4-RD, ruled out malignancy/infection	3 (12%)
Met Clinical Criteria for IgG4-RD (of those not biopsied)	2 (8%)
Presentation	
Pain (back or flank)	19 (73%)
Renal Failure	16 (62%)
Treatment Approach	
Prior Treatment with Steroids	10 (39%)
Rituximab with Steroids	6 (23%)
Rituximab Only	20 (76%)
Ureteral Stents or Percutaneous Nephrostomy (PCN) Tube	10 (39%)
Treatment Response	
Symptomatic Response (N=26)	21 (100%)*
Radiographic Response** (N=25)	22 (88%)†
Stable (if no reduction in size, N=3)	3 (100%)
Stent or PCN Removed (N=10)	4 (40%)††

*of those with baseline symptoms; **Response defined as improvement in size in at least 2 planes (e.g., anterior-posterior, cranio-caudal); †of 25 patients with f/u radiology; ††of 10 patients with stents or PCN

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Samantha L. Walsh, B.S., Psychiatry

Suicidal Ideation as Impaired Present Bias in Decision Making

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Introduction: Bipolar disorder (BD) is a chronic psychiatric condition often associated with suicide attempts. The pathophysiology underlying decision making related to suicide is unknown. Present bias is the tendency to choose less money now ("shorter-small" reward) instead of (waiting for) more money later ("larger-later" reward). Neuroimaging studies show that present bias is related to increased ventral striatum, medial frontal gyrus, and posterior cingulate activation in response to immediate rewards in healthy individuals. Increased dorsolateral prefrontal cortex and posterior parietal activation is found in response to choosing delayed rewards. Research has shown that present bias can be altered if participants are primed with affective information. For example, individuals who underwent a positive emotion induction were more likely to choose more delayed, larger rewards compared to sooner, smaller rewards (Pyone & Isen, 2011). In a non-clinical population, sadness has been shown to increase present bias, creating a phenomenon termed "myopic misery" (Lerner et al., 2013). Being able to decide between immediate versus future rewards requires self-control and consideration of the future. Due to the presence of sadness in BD, this primed affective information effect on present bias may be particularly pronounced in bipolar patients with suicidal ideation. In the present study, we examined present bias and associated brain activity in suicidal bipolar patients. We hypothesized that present bias would increase in the sad as opposed to the neutral conditions. We also expected to see increases in BOLD activation in the brain regions associated with present bias in the sad condition as compared to neutral.
Methods: Fifteen bipolar patients (8 female, M_{age}=37.6 ± 14.3 years) with DSM-IV BD completed a present bias paradigm during neutral and sad mood states (Lerner, Li, & Weber, 2013) while undergoing functional magnetic resonance imaging (fMRI) using a Siemens 3.0 Tesla Skyra scanner (TR=2560, TE=30). Suicidality was assessed using the Columbia Suicide Severity Rating Scale (C-SSRS). During scanning, subjects underwent two emotion inductions, first neutral then sad. Each

emotion induction was followed by 42 trials in which subjects chose between receiving a smaller amount of money ($11-$80) now or a larger amount of money ($25-$85) at a delay of 2, 4, 6, or 8 weeks. Behavioral data during the task was fit to a quasihyperbolic discounting function using maximum-likelihood estimation, estimated separately for neutral and sad inductions. This model yields the probability that a subject will choose the delayed reward for each trial. This value, multiplied by the monetary value of the reward, yields the subjective value of that reward. Imaging data was processed using SPM8; first level models examined differences between sad and neutral states for both immediate and delayed rewards. Parametric trial by trial regressors were used to represent the utility surplus of the reward chosen (subjective value of the reward not chosen subtracted from the reward chosen). For the second level multiple regression analysis, the C-SSRS Lifetime Suicidal Ideation Intensity subscale was used as a regressor of interest. Imaging results with a $p \leq .01$ uncorrected will be reported.

Results: Participants showed an increased present bias during sad compared to neutral state ($p<.05$), reflecting an increased likelihood to choose smaller rewards sooner rather than larger rewards later when sad. Compared to the neutral condition, sad state fMRI results showed that when subjects selected the immediate reward, C-SSRS scores correlated positively with activity in the anterior cingulate cortex, precuneus, posterior parietal lobes, and anterior insula and negatively with activity in the medial frontal gyrus, superior frontal gyrus, and posterior cingulate cortex.

Conclusion: As SI intensity increases, sad mood induction as opposed to neutral mood induction in bipolar patients was associated with greater activation in regions related to emotion regulation and reward, and decreased activation in regions involved in decision making. These findings suggest that bipolar patients may be more prone to SI due to biologically driven increases in present bias. Future studies are needed to see how this affective priming affects brain activation during present bias in healthy controls.

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Shirley L. Wang, B.S., Surgery - Burn

Comparison of Burn Outcomes Questionnaire Results in Two Cohorts with Electronic and Paper Methods of Administration

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Introduction: The Burn Outcomes Questionnaire (BOQ) is an extensively validated measure that assesses the psychosocial and physical recovery of patients across twelve domains. Beginning nearly twenty years ago, a Benchmarking study collected BOQ surveys prospectively over several years of follow-up from more than one thousand patients (The Multi-Center Benchmarking Study). While the BOQ has proven to be a useful research tool, with more than a dozen published papers describing its use for that purpose, use of the BOQ in clinical settings has just begun. Over the past few years, as part of a study investigating the usefulness of a system for feedback of patient-reported outcome measures (PROMs) to clinicians and patients, administration of BOQ surveys was included as part of routine clinical care. This study was conducted in an outpatient burn clinic, with parents filling out the questionnaire on an iPad and clinicians receiving scored output from the BOQ prior to their encounter with the patient. Because the Benchmarking study validated the BOQ in a paper and pencil format, the current study compared results from electronic and paper and pencil versions of the BOQ.

Methods: In the current study, the BOQ for children aged 5-18 years (BOQ_{5-18}) was administered to parents of children receiving treatment for burn injuries at a regional burn center. To be included in the Feedback cohort with iPad administration, children had at least a 5% total burn surface area (TBSA) or a burn to a critical area (face, hands, feet, or genitalia). The electronic BOQ was administered to parents of children using the HIPAA-compliant Tonic© software on iPads. In the original Benchmarking study, the BOQ_{5-18} was administered using similar criteria for burn size and location. Although four burn centers participated in the Benchmarking study, only patients from the Boston hospital were included in order to maximize congruency with the Feedback study sample. Analysis of aggregated data from the Benchmarking and Feedback cohorts explored the validity of the new electronic delivery mode of the questionnaire by comparing the average subscale scores from the two cohorts.

Results: BOQ forms were available for 187 Boston patients in the Benchmarking cohort and 82 patients in the Feedback cohort. Patients in the Feedback cohort were significantly older, were further removed in time from their burn injuries and had smaller burns. The mean age of patients in the Benchmarking cohort was 9.5 ± 4.2 years and patients had experienced their burn injury 1.2 ± 1.6 years prior to the date of survey. Patients included in the Feedback cohort were on average 11.5 ± 4.1 years of age and had experienced their injury 2.8 ± 4.1 years before the survey. The mean TBSAs for the Benchmarking and Feedback cohorts were 24.4 ± 22% and 15.0 ± 20%, respectively. Another way to explore the impact of burn severity is to recode TBSA into small, medium, and large burn categories. Although a comparison of the two cohorts failed to show

a statistically significant difference in the burn size categories, the pattern found with TBSA was again present, with fewer small and a greater number of large burns in the Benchmarking cohort. In this cohort, 63% were coded as having a small TBSA (<25%), 24% had a medium TBSA (25-49.99%), and 13% had a large TBSA (≥50%) in comparison with the Feedback cohort where seventy-six percent had a small TBSA, 14% had a medium TBSA, and 10% had a large TBSA. On each of the twelve BOQ subscales, the percentages of patients coded as "at risk" were similar between the Benchmarking and Feedback cohorts. The rates of patients "at risk" among each cohort did not vary significantly for the following subscales: pain, physical function and sports, upper extremity function, transfers and mobility, appearance, emotional health, and school re-entry. On five of the subscales, however, children in the Feedback cohort were significantly less likely to be at risk on the following domains: itch ($p<0.05$), compliance ($p<0.05$), parental concern ($p<0.05$), family disruption ($p<0.001$), and satisfaction with current state ($p<0.001$).

Conclusion: Results from the current study suggested that the profile of risk on the BOQ subscales was similar in the two cohorts, despite the significant differences in age, burn size, and years since burn. The rates of risk differed significantly between the two cohorts on only five of the twelve subscales. On two of the subscales (Itch and Compliance) the difference in the percentage of patients at risk was about 10% or less. Larger differences in risk were observed on the Family Disruption, Parental Concern, and Satisfaction with Current State subscales. Since these differences could easily be attributable primarily to the larger time since burn and smaller burn size in the Feedback study cohort, it seemed likely that rates of risk on the subscales of the iPad-administered BOQ would be reasonably comparable to those obtained using BOQ surveys administered by paper and pencil. A study in progress will match cases from the two groups using propensity analysis so that confounding variables such as demographics and clinical variables including burn size and years since burn can be controlled for and thus provide a more definitive comparison of risk rates based on the differing methods of BOQ administration. With our current analyses, however, it appears that the electronic version of the BOQ will yield results comparable to and congruent with those obtained through the paper and pencil version.

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Zongwei Wang, PhD, Urology

Androgenic to Estrogenic Switch in Human Adult Prostate Gland as a result of Epigenetic Silencing of Steroid 5-α Reductase 2

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Introduction: The steroid 5-α reductase type 2 (SRD5A2) is critical for prostatic development and growth. Strategies to block SRD5A2 using 5-alpha reductase inhibitors (5ARI) remain a mainstay in the treatment of benign prostatic hyperplasia (BPH). However, one-third of men are resistant to 5ARI therapies. We previously showed that expression of SRD5A2 is not static, since epigenetic modulations by DNA methyltransferase and pro-inflammatory cytokines somatically silence SRD5A2 during adulthood. Here we wished to identify whether absence of prostatic SRD5A2, when androgenic pathways are blocked, leads to modification of alternate hormonal pathways.

Methods: Prostatic samples were obtained from patients with symptomatic BPH undergoing transurethral resection of prostate (TURP) surgery. Prostatic protein expression of SRD5A2, androgen receptor (AR), estrogen receptor (ER) subunits, and aromatase were determined by Western blot, immunohistochemistry (IHC), and ELISA assays. Prostatic levels of testosterone (T), dihydrotestosterone (DHT), estradiol (E) were measured by HPLC-MS. In *in vitro* study, primary prostatic stroma cells and epithelial cells BPE and BPH-1 were cultured and treated with TNF-α, and the expression of aromatase were determined by qPCR and ELISA.

Results: In prostate specimens that were methylated at the SRD5A2 promoter locus, estrogen response genes are among the most significantly upregulated genes in prostate samples that are methylated at the SRD5A2 promoter locus. The levels of T, E and aromatase were significantly upregulated, while DHT was significantly decreased. The ratio of T/E was significantly lower. DHT was inversely correlated with T levels, and aromatase was negatively correlated with DHT. Absence of SRD5A2 significantly upregulated the phosphorylation of ERα (pERα), but did not significantly affect the levels of total ERα, total ERβ or pERβ. In primary prostatic stromal cells, the aromatase levels were significantly increased with TNF-α treatment alone or when expression of SRD5A2 was suppressed by siRNA transfection. Treatment of prostatic epithelial BPH-1 cells with TNF-α did not change the androgenic or estrogenic signalling, but the aromatase levels in stromal cells were significantly upregulated when treated with TNF-α and cultured in BPH-1 conditioned media.

Conclusion: Our study demonstrates for the first time that there is an androgenic to estrogenic switch when SRD5A2 is absent in the prostate gland. Somatic epigenetic silencing of SRD5A2 changes the prostatic hormonal milieu, and may modulate prostatic homeostasis and growth. ER modifiers may prove to be better therapeutic options in carefully selected patients who lack SRD5A2 expression for management of prostatic diseases.

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Jason H. Wasfy, MD MPhil, Massachusetts General Physicians Organization (MGPO)

Variation in the echocardiographic surveillance of primary mitral regurgitation

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Introduction: Clinical outcomes after surgical treatment of mitral regurgitation (MR) are worse if intervention occurs after deterioration of left ventricular (LV) size and function. Trans-thoracic echocardiographic (TTE) surveillance of patients with MR is indicated to avoid adverse ventricular remodeling. Overly frequent TTEs can impair patient access and reduce value in care delivery. This balance between timely surveillance and over-utilization of TTE in valvular disease provides a model to study variation in the delivery of health care services. We investigated patient and provider factors contributing to variation in TTE utilization, and hypothesized that variation was attributable to provider practice even after adjustment for patient characteristics.
Methods: We obtained records of all TTEs from 2001-2016 ordered at a large echocardiography laboratory. The outcome variable was time interval between TTEs. We constructed a mixed-effects linear regression model with the individual physician as the random effect in the model, and used intra-class correlation coefficient (ICC) to assess the proportion of outcome variation due to provider practice.
Results: Our study cohort was 55,773 TTEs corresponding to 37,843 intervals ordered by 635 providers. The mean interval between TTEs was 12.4 months, 17.0 months, 18.3 months, and 17.4 months for severe, moderate, mild, and trace MR respectively, with 20% of providers deemed over-utilizers of TTEs, and 25% under-utilizers.
Conclusion: We conclude that there is substantial variation in follow-up intervals for TTE assessment of MR, despite risk-adjustment for patient variables, likely due to provider factors. These results provide guidance about how to improve quality and value for patients with primary mitral regurgitation.

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Jason H. Wasfy, MD, M.Phil., Performance Analysis and Improvement/Practice Improvement

Longer Term Impact of E-Consults

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Introduction: From 1999-2010, there was a 21% increase in annual visits/1,000 to specialists, compared to a 12% annual increase among generalists in the same period. We'll share highlights of our four published manuscripts, as well as soem more recent studies, describing our pilot approach, explosive growth, results, and areas where further investigation is needed. We'll share some background on how and why the E-Consult pilot program was started at MGH, describe the healthcare challenges being addressed, and share the measures developed to monitor program operations and impact on care delivery.
Methods: E-Consults are an innovative way to deliver outpatient specialist care, helping to reduce unnecessary specialist utilization and improve access to care for our sickest patients. Our MGH E-Consult pilot program experienced considerable growth in 2015 and 2016, with successful transition from CRMS, a home-grown system, to a custom Epic build that went live in April 2016. Mid-way into CY2017, we've seen even more explosive growth. We continue to see increased provider participation within MGH and increasing participation across the Partners network, and are developing plans to further increase service offerings in new adult and pediatric specialty areas where we see demand. With this program, PCPs or other care providers initiate an E-Consult order in Epic, and then receive structured guidance from a specialist within 2-3 days. This provides more rapid access to specialist expertise compared with waiting for a traditional office visit to implement the optimized course of treatment.
Results: By the end of June 2017, approximately 7,500 E-Consults have been completed by 115+ MGH specialist providers across 31 service areas since the program began in December 2013. The program has become part of standard workflow for many providers, and continues to grow. In particular, for specialties with an active E-Consult service, we've seen nearly 5% (for some areas up to 18%) of referrals were submitted as E-Consults. Preliminary analysis in late 2016 found approximately 80% of E-Consults avoided an unnecessary visit. More recent findings from a limited study show E-Consults are reducing unnecessary traditional referrals to cardiology for strong adopters of E-Consults, thereby improving access, quality, value, and satisfaction.
Conclusion: E-Consults are an effective and safe mechanism to enhance value in outpatient cardiology and other specialties as well, with low rates of bounceback to traditional consults. WE've seen CArdiology E-Consults can account fro nearly

one-tenth of outpatient consultation over one year within an ACO, and are associated with reduction in traditional referrals to cardiologists. E-Consults offer a genuine transformation in outpatient specialist care delivery at the MGH. Our team has published four manuscripts on our results, with others being drafted, and is frequently asked to share our experiences and advice externally. Our work has influenced the delivery of specialist care throughout the country.

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Ana Weil, MD MPH, Medicine - Infectious Diseases

The Gut Microbiome and Susceptibility to *Vibrio cholerae* Infection

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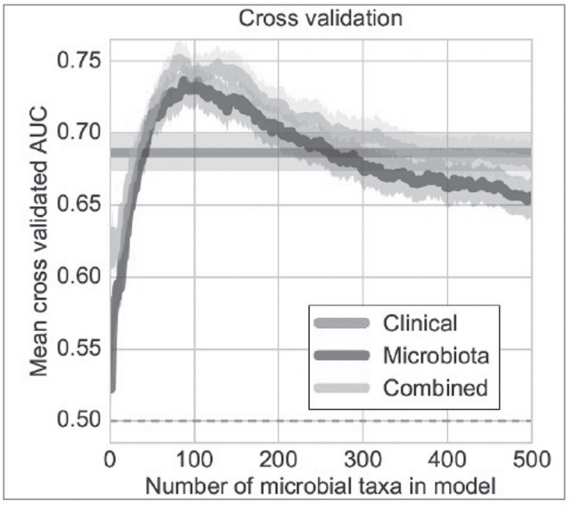
Introduction: In endemic and epidemic patterns of cholera transmission, multiple *Vibrio cholerae* infections within the same household are common. Prospective observation of household contacts exposed to *V. cholerae* has identified clinical and epidemiologic factors that correlate with susceptibility to infection, including young age, blood group O, and lack of pre-existing immunity to *V. cholerae*. These factors only partially explain the infections observed in cohorts of household contacts of cholera patients. Animal studies suggest that the gut microbiota may impact *V. cholerae* virulence, and the clinical relevance of these findings has not been tested. We prospectively studied household contacts of cholera patients and identified associations between the gut microbiome at the time of exposure to *V. cholerae* and the likelihood of subsequently developing infection.

Methods: This study was conducted in collaboration with the International Centre for Diarrheal Disease Research, Bangladesh, Dhaka Hospital. Household contacts of patients presenting with acute watery diarrhea and a stool culture positive for *V. cholerae* as the sole pathogen were eligible. At the time of enrollment (day 2), and during follow up, contacts were questioned about diarrhea, and rectal swabs were collected at daily home visits. Serum immune responses to *V. cholerae* were evaluated at baseline, and at days 7 and 30. Contacts were categorized as those who developed definite infection (positive rectal swab culture for *V. cholerae* or serologic change plus diarrhea) during the follow-up period and those who had no evidence of infection. Bacterial DNA was isolated from rectal swabs, the V4 region of bacterial 16S rRNA was amplified, and sequencing was performed on an Illumina Miseq platform. Sequences were processed using the Quantitative Insights into Microbial Ecology program and classified into related groups of bacteria termed operational taxonomic units (OTUs). To identify associations between specific OTUs and clinical outcomes, we used a supervised learning method that creates a geometric rule for separating two classes of variables based on prominent features of the two classes (household contacts with definite infection versus household contacts with no evidence of infection) plotted in a multidimensional space. Cross-validation was used to test how well the OTUs predicted susceptibility to infection. In cross-validation, we held out 10% of the samples (8 samples) and develop a classification model on the remaining 90% of the samples (68 samples), referred to as the training set. Numerous iterations of this exercise were performed to reduce variability and estimate model prediction performance.

Results: Rectal swabs from 76 participants were included in the final analysis. We found that OTUs identified in rectal swabs of household contacts on day 2 could predict *V. cholerae* infection with an area under the curve (AUC) of 0.74 using 88 taxa (microbiota model, Fig 1). This improves upon the predictive power of susceptibility using the previously known clinical and epidemiologic factors (clinical model, Fig 1). The phylum *Bacteroidetes* was more abundant in the contacts who were protected from infection, and specific *Blautia* species were more likely to be found in samples from protected household contacts. An increase in specific *Streptococcus* and *Prevotella* species were found in rectal swabs of contacts who developed infection. The species *Paracoccus aminovorans* was more abundant in the household contacts with infection at the time of enrollment. *In vitro,* we found that in the presence of *P. aminovorans* supernatant, *V. cholerae* demonstrated enhanced growth, suggesting a potential interaction between these species that may influence clinical outcomes.

Conclusion: The gut microbial population present at the time of exposure to *V. cholerae* is predictive of infection. The observed correlation between the gut microbiome and susceptibility to *V. cholerae* could be the result of direct competition between microbes or due to metabolites of gut bacteria that influence *V. cholerae* growth or virulence factor expression. The biological interaction between specific bacterial groups and *V. cholerae* warrants further study.



Predictive model performance. Model was tested using a cross-validation scheme, in which contacts were repeatedly split into training and testing sets. AUC scores are shown as a function of microbial taxa included in the model. The clinical model represents epidemiologic and clinical factors known to contribute to susceptibility. Bold lines represent the mean cross-validated AUC and shaded bands represent the standard error of the mean. The microbiota based model reached maximum performance at 88 OTUs (AUC=0.74; P<0.01). The dashed gray line indicates theoretical performance of the model randomly guessing subject susceptibility.

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Amy M. West, MD, EdM, Physical Medicine and Rehabilitation

Softball windmill pitchers: strength and motion in the dominant versus non-dominant upper and lower extremity

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Introduction: For more than 20 years, fast- pitch softball has been amongst the largest team sports in the US with over 35 million participants. It is one of the fastest growing sports for women with more than 2 million females between the ages of 12 and 18 competing and over 14,000 high school teams nationwide. There are currently no limits on innings or pitch counts despite reports that female softball players sustain a significantly higher injury rate than males participating in baseball. Studies have shown that stresses that occur with windmill-style pitching are comparable to those reported during baseball. Given the relatively high number of pitches thrown by softball pitchers, we need a better understanding of risk of injury and injury pattern. Our objective was to assess differences between dominant and non-dominant (ND) shoulder, elbow and hip (lead and trail leg) strength and range of motion (ROM) in high school (HS) and collegiate level softball windmill pitchers.
Methods: Thirty-three female softball pitchers (24 HS, 9 collegiate) were recruited from local softball teams. Handheld dynamometer strength and goniometric joint ROM of the shoulder, elbow and hip were measured.
Results: Across all pitchers ROM measures demonstrated greater shoulder flexion ROM (p=.004) in the ND than the in the throwing arm. There was greater hip extension ROM in the lead leg than trail leg (n=25), p= .02. Among HS pitchers, there was greater shoulder external rotation ROM (ER) (x=107.32±6.67) than collegiate pitchers (x=100.1 ±6.92). There was greater elbow extension ROM in HS pitchers (x= +4.84±2.91) than collegiate players (x= +2.00±2.65), p= .02. There was no difference in total arc of shoulder rotational motion (ER+internal rotation (IR)) between dominant and ND arms across all pitchers, nor between HS and collegiate pitchers. Strength measures demonstrated greater throwing arm shoulder abduction (p=.026) and IR strength (p=.001) than the ND shoulder across all pitchers. No differences noted in hip strength between lead and trail legs.
Conclusion: Female windmill pitchers are not well studied. This study reports side to side differences in ROM and strength in a sample of HS and collegiate softball pitchers. By establishing baseline characteristics, providers can assess players and determine if ROM and strength differences are abnormal. Published measures for baseball pitchers have influenced injury prevention and training programs. Further investigation of softball pitchers is needed to determine if abnormal findings are beneficial adaptations that may improve performance, or risk factors for injury that require treatment or new training programs.

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Sarah E. Wicheta, Oral and Maxillofacial Surgery

The minor salivary gland biopsy: an important tool in the diagnosis of Sjogren's syndrome

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Introduction: Sjogren's syndrome (SS), though commonly associated with xerostomia and xerophthalmia, may present with extraglandular manifestations that make definitive diagnosis difficult. The two leading diagnostic classification systems both include a positive minor salivary gland biopsy (MSGB) as a major inclusion criteria.[1] Our purpose is to better define the role of the MSGB in establishing a diagnosis of SS in a cohort of referred patients.
Methods: This is a retrospective cohort study of patients referred to the Massachusetts General Hospital (MGH) Department of OMFS over a 5 year period to establish a diagnosis of SS. Inclusion criteria were: complete information regarding presenting symptoms, reason for referral and findings on MSGB. Incomplete records and referral for reasons other than presumptive SS resulted in exclusion. The MSGB and its role in definitive diagnosis based on accepted classification systems is evaluated for sensitivity, specificity and positive and negative predictive value. Other variables of interest (demographics, pattern of referral and symptomology) are described for the cohort.
Results: A total of eighty- seven patients met inclusion criteria. The mean age was 48.3 years (range 19-74 years) and 75 (86.2%) were female. Fifteen MSGB (17.2%) were positive based on the focus score (FS) histologic criteria.[2] In 12/15 cases, it was the positive MSGB that allowed for definitive diagnosis (80%). In 3 cases, other criteria allowed diagnosis without the contribution of the MSGB. (Sensitivity of MSGB=80.0%; Specificity=87.5%; Positive Predictive Value=57.1%; Negative Predictive Value=95.5%)
Conclusion: The MSGB is an important contributor to a diagnosis of SS. When serology was negative, the MSGB was often the criterion that allowed the diagnosis to be established. It is the most frequently positive of the major criteria employed by both classification systems in current use.

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Sarah T. Wieman, B.A., Psychiatry

Psychosocial Factors Associated with Quality of Life in Generalized Anxiety Disorder: The Role of Perceived Stress, Sleep Quality, and Mindfulness

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Introduction: Generalized Anxiety Disorder (GAD) is associated with poorer quality of life (QoL). Higher levels of mindfulness, better sleep quality, and lower perceived stress have been positively associated with QoL. Those with GAD exhibit less mindfulness, poorer sleep quality, and higher perceived stress than non-clinical populations; it is unknown, however, which of these variables are associated with the specific domains of QoL as presented in the World Health Organization Quality of Life questionnaire (WHOQOL): physical, psychological, social, and environmental. The present study examined the relative, independent associations of mindfulness, sleep, and perceived stress with QoL in a sample of adults with a primary diagnosis of GAD.
Methods: Treatment seeking adults (n=152, mean(SD) age= 33 (12.8) years, 73% (n=111) female) with a primary diagnosis of GAD as determined by a structured clinical interview completed the Five Facet Mindfulness Questionnaire (FFMQ; Baer et al., 2006), Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1988), Perceived Stress Scale (PSS; Cohen, et al., 1983), Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A; Shear et al., 2001), Beck Depression Inventory-II (BDI-II; Beck et al., 1996), and the WHOQOL (Skevington et al., 2004) at baseline of a treatment study for GAD. Multiple regression analyses examined the associations of the FFMQ, PSQI, and PSS with the four domains of the WHOQOL, while controlling for BDI-II and SIGH-A.
Results: The psychosocial predictors accounted for a significant proportion of the variance in each of the QoL domains (psychological: 58%, social: 21%, physical: 44%, and environment: 26%, all p's <.05). The PSS showed independent associations with poor QoL across all subscales (physical: β= -.22; psychological: β= -.39; social: β= -.24; environment: β= -.24; all p's <.05). Additionally, FFMQ and PSQI were independently associated with the following subscales: FFMQ: β= .16 psychological, and β= .18 social; PSQI: β= -.29 physical; and β= -.16 environment (all p's <.05).
Conclusion: Mindfulness and sleep are associated with QoL. Moreover, perceived stress is significantly associated with all types of QoL, suggesting that decreasing perceived stress may be an important therapeutic target in GAD.

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Timothy Wilens, Psychiatry

A Case Series of Omega-3 Fatty Acids Supplementation in Medicated Children with Attention Deficit Hyperactivity Disorder and Deficits in Emotional Self-Regulation

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Introduction: Recent work has demonstrated that treated and untreated individuals with attention deficit hyperactivity disorder (ADHD) have elevated rates of deficits in emotional self-regulation (DESR). However, few treatment options specifically targeting DESR in ADHD exist. Omega 3 fatty acids have been shown to reduce mood dysregulation. We aimed to evaluate the effectiveness of adjunct omega-3 fatty acids treatment in children with co-occurring ADHD and DESR.
Methods: Children aged 6 to 17 years who carried an established diagnosis of ADHD and were receiving medication for their ADHD prior to screening were enrolled. Omega-3 FA (975 mg EPA) was administered openly up to 12 weeks supplemental to subjects' ADHD medication. Primary outcomes included Clinical Global Impression (CGI) scales for ADHD and DESR, and the Behavior Rating Inventory of Executive Functioning (BRIEF-P). All analyses were intention to treat with the last observation carried forward for subjects that did not complete the full study schedule. A series of paired sample t-tests were conducted to compare the pre- and post-treatment scores of the outcome measures. All tests were 2-tailed, and significance was determined at $\alpha = 0.05$.
Results: Twenty-one subjects signed consent and were enrolled. Of those that enrolled, several did not participate after signing consent (n=7), were lost to follow-up after the baseline visit (n=1), or discontinued by the investigator due to protocol requirements (n=2). Our final sample (n=10) included 7 subjects who completed the study, and 3 subjects who finished study measures through week 6 of the 12-week trial (60% male; mean age 10.6 ± 2.6 years). By CGI-Improvement, 70% of subjects were DESR "responders" with reduced CGI-DESR Severity scores (4.6 ± 0.7 to 3.0 ± 0.9; $p<0.0001$). While we found improvement trends on the major indices of the BRIEF-P; there was no significant improvement in ADHD. Overall, the omega-3 fatty acids were well tolerated.
Conclusion: Our findings from small case series of omega-3 fatty acids supplementation to ADHD medication in children with ADHD and DESR, showed improvements in mood (DESR) but not ADHD. These pilot data provide encouraging support for a larger controlled trial of Omega-3 fatty acids as adjunct therapy for residual DESR in treated ADHD youth.

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Victoria J. Williams, PhD, Neurology

Task-related fMRI activation during a hyperinsulinemic-euglycemic clamp procedure

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Introduction: A growing body of evidence suggests significant overlap in risk, co-morbidity, and putative pathophysiological mechanisms across Type 2 Diabetes and Alzheimer's Disease. Although the effect of systemic insulin resistance on peripheral tissue is well-studied, the degree to which insulin impacts brain tissue in vivo remains unclear. To address this knowledge gap, we utilized an insulin clamp technique to continuously increase plasma insulin concentrations while maintaining normal blood glucose levels during task fMRI, thereby permitting investigation into the real-time effects of hyperinsulinemia on brain function.
Methods: Four healthy adults (aged 59 - 79) completed 3T functional MRI while simultaneously undergoing a hyperinsulinemic-euglycemic clamp procedure under two experimental conditions: infusion of single blinded insulin infusate and infusion of single blinded placebo saline. During each visit, participants performed two runs of an fMRI "N-back" task to investigate within- and between-subject differences in neural activation across experimental conditions.
Results: Behaviorally, reaction time was significantly slower on 2-back trials during the insulin compared to placebo condition ($p < 0.05$). Using FSL, we also observed a significant increase in average within-subject fMRI brain activation on the N-back task (2-back>0-back contrast) during the insulin clamp compared to placebo condition in bilateral middle/inferior frontal, occipito-parietal, and precuneus cortices, bilateral thalamus, and left parahippocampal regions (all $p < 0.01$, corrected).
Conclusion: We found that experimentally-induced hyperinsulinemia in the setting of euglycemia in healthy participants leads to real-time differences in cognitive performance and fMRI-indexed brain activation. Findings of increased reaction time, coupled with a greater degree of task-related fMRI activation, suggest that abnormaly elevated insulin levels may contribute to more effortful processing in the context of cognitively demanding tasks.

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Loren Winters, MSN, Medicine - MGH Cancer Center

Development, Feasibility and Use of an Internet-Streamed Yoga Intervention for Breast Cancer Survivors

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Introduction: Prior research has demonstrated that Yoga reduces fatigue and stress in women with early stage breast cancer. Although hospitals offer yoga therapy programs, many patients do not return to participate. An Internet streamed hospital sponsored yoga video may provide an alternative but research is needed to determine patients' responses. The purpose of this study is to describe breast cancer survivors' responses to a Cancer center team developed Internet-streamed yoga video.
Methods: Qualitative content analysis of post intervention telephone interviews. A gentle yoga sequence that incorporated postures similar to stretches prescribed post-operatively was adapted for video self usage. Patients with early stage estrogen receptor positive breast cancer, within one year of initiating adjuvant endocrine therapy, were recruited by their oncology providers during routine visits. Consenting participants received an email link to the 17 minute video intervention, and asked to use it twice weekly for four weeks. Telephone debriefing interviews followed.
Results: Fourteen post-menopausal women, on average age 58 and Caucasian, met the eligibility criteria and participated. Most had no prior yoga experience. Overall, participants had no difficulty viewing the video at home, using it on a smart phone or tablet device, and found streaming convenient. Most found the video enjoyable but did not use it more than once or twice after the first week. Many were unsure whether yoga helped reduce their most distressful symptoms which were mental/emotional stress and surgical pain. Some described needing more instruction about what yoga is and how to best use it for self-care. All liked talking with the nurse during the follow-up calls.
Conclusion: Findings from this pilot study suggest that an Internet-streamed yoga intervention was accepted by participants as a feasible means to access a yoga self-care intervention but more tailored motivational instruction is needed to promote usage. Future research is needed to optimize video content and patient usage.

Cancer Center Yoga

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Kelley A. Wittbold, MD, Emergency

ED-to-ICU Return Admissions: A Better Surrogate Measure for Quality Assurance in the Emergency Department

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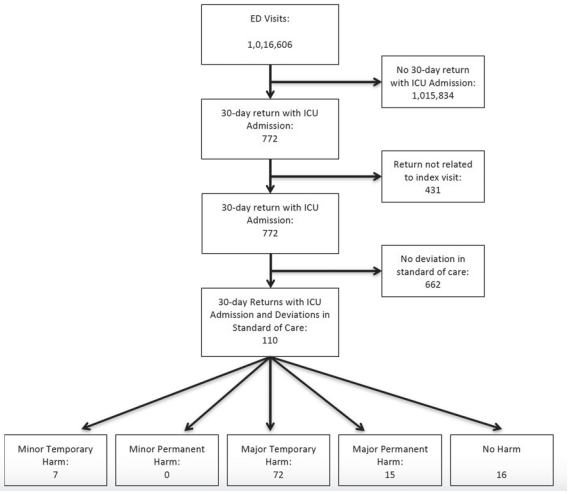
Introduction: Patients who return to the Emergency Department (ED) and require admission is often seen as a surrogate for quality and used for Quality Assurance efforts. Despite this, recent study has suggested that this is low yield for identifying errors. We hypothesize that patients who return and are admitted to the ICU are more likely to represent medically complex patients with opportunities for improvement on their first visit. The objective of this study was to identify the prevalence of error deficient care in patients who return and require ICU admission, as well as the types and severity of harm in these patients.

Methods: Retrospective review of all patients who presented to an urban, university affiliated ED between January 1, 2005-December 31, 2015 who were evaluated, discharged, and returned within 30 days requiring ICU admission. An ED physician reviewer traced the care through a defined sequence of diagnostic steps. If an error was judged to have been present in any of these steps, the reviewer further classified the deviation in care and assigned a severity score.
Results: There were 1,016,606 ED visits during the 10 year study period, with 772 patients who were seen in the ED and then returned within 30 days requiring ICU admission (0.0076%). 341 of these patients were deemed to have a return visit related to the index visit. Of these, 11O cases (32.2%) were felt to represent a deviation from optimal care. When a standard diagnostic process of care framework was applied to these 110 encounters, the majority of cases represented failures in the initial diagnostic pathway (60 cases, 54.5%), including a failure to obtain a complete history and conduct a complete physical exam (13 cases, 11.8%), failure of ongoing monitoring of clinical status (3 cases, 2.7%), failure to establish a differential diagnosis (20 cases, 18.2%) and failure to order the appropriate diagnostic test (24 cases, 21.8%). The remainder of the cases represented failures in completing testing and results processing (23cases, 20.9%), and failures in follow up and coordination (27 cases, 24.5%). When the National Patient Safety Foundation's Error Severity Codes were applied to the 110 cases that represented deviations from optimal care, no harm in 16 (14.5%), 7 (6.4%) resulted in minor temporary harm, 72(65.5%) in major temporary harm, 0 (0%) in minor permanent harm and 15 (13.6%) in major permanent harm. The most commonly missed diagnosis on initial visit where harm was attributed was an infectious disease diagnosis 72 (21.1%).
Conclusion: Standard screening methodology of ICU returns resulting in admission has a higher yield in identifying suboptimal care than 72 hour returns, with 32.2% of cases reviewed representing deviations from standard care. Of these, the vast majority represent cognitive errors in the diagnostic pathway. Future study should focus on understanding the yield of other departmental QA triggers such as Safety Reports and Morbidity and Mortality Conferences.



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Rebecca Wolenski, Bachelor of Science, Psychiatry

Similar Familial Underpinnings for Full and Subsyndromal Pediatric Bipolar Disorder: A Familial Risk Analysis

J. Wozniak[1,2], M. Uchida[1,2], S.V. Faraone[3], M. Fitzgerald[1], C. Vaudreuil[1,2], N. Carrellas[1], J. Davis[1], R. Wolenski[1] and J. Biederman[1,2]

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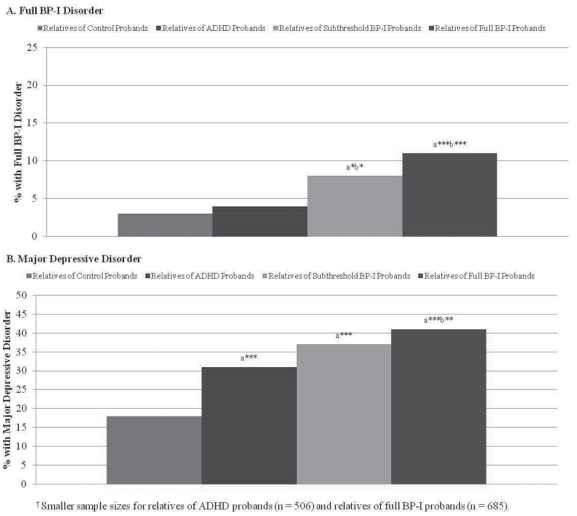
Introduction: Pediatric bipolar (BP)-I disorder is a highly morbid and disabling neurobiological disorder estimated to afflict 1-2% of children. Because of its insidious onset over many years, subsyndromal manifestations of BP-I disorder often precede the child's development of the full syndromatic state. Yet, severe criticism has been leveled against subsyndromal manifestations of pediatric BP-I disorder. For example, the subthreshold diagnoses was first termed a "catch-all" category that results in "a loss of important clinical information" (1). While these concerns are rampant in pediatric psychiatry, the clinical relevance of subthreshold diagnoses is recognized as critically important in adult psychiatry. Given the genetic underpinnings of BP-I disorder (2) and the recognition that gene expression can result in full or partial manifestations of the clinical liability, family studies can help verify the validity of subthreshold cases of pediatric onset bipolar-I disorder so that it may be considered equally important in this younger population.

Methods: BP-I probands were youth aged 6–17 years meeting criteria for BP-I, full (N=239) or subthreshold (N=43), and also included were their first-degree relatives (N=687 and N=120, respectively). Comparators were youth with ADHD (N=162), controls without ADHD or bipolar disorder (N=136), and their first-degree relatives (N=511 and N=411, respectively). We randomly selected 162 non-bipolar ADHD probands and 136 non-bipolar, non-ADHD control probands of similar age and sex distribution to the BP-I probands from our case–control ADHD family studies. Psychiatric assessments were made by trained psychometricians using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Epidemiological Version (KSADS-E) and Structured Clinical Interview for DSM-IV (SCID) structured diagnostic interviews. We analyzed rates of bipolar disorder using multinomial logistic regression.
Results: Rates of full BP-I significantly differed between the four groups (χ^2_3=32.72, P<.001): relatives of full BP-I probands and relatives of subthreshold BP-I probands had significantly higher rates of full BP-I than relatives of ADHD probands and relatives of control probands. Relatives of full BP-I, subthreshold BP-I, and ADHD probands also had significantly higher rates of major depressive disorder compared to relatives of control probands.
Conclusion: Results from this familial risk analysis showed that youth with subthreshold BP-I disorder had similarly elevated risk for BP-I disorder and MDD in first-degree relatives as youth with full BP-I disorder. These findings support the diagnostic continuity between subsyndromal and fully syndromatic states of pediatric BP-I disorder. The identification of subsyndromal manifestations of pediatric BP-I disorder has important clinical, scientific, and public health implications. Irrespective of whether subsyndromal manifestations of BP-I disorder represent early stages of BP-I disorder or a forme fruste of BP-I disorder, it is equally important to identify and address subsyndromal forms of BP-I disorder due to their associated morbidity and dysfunction, as well as their risk for conversion to fully syndromatic states, as an attempt to interrupt the progression of the illness. Targeting subsyndromal manifestations of BP-I disorder for neurobiological studies could provide critical insights as to the underlying neurobiological underpinnings of the disorder without the confounders of chronicity and treatment.

Figure 1. Rates of full BP-I disorder and major depressive disorder among relatives of control, ADHD, subthreshold BP-I, and full BP-I probands. A. Full BP-I disorder. B. Major depressive disorder.
[a] Compared to relatives of control probands. [b] Compared to relatives of ADHD probands. *P<0.05, **P<0.005, ***P<0.001



[1] Smaller sample sizes for relatives of ADHD probands (n = 506) and relatives of full BP-I probands (n = 685).

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Alice Won, B.S., Emergency

Orthopedic surgical procedures supported by a Ketamine package when no anesthetist is available: A series of 345 cases from rural Kenya

A. Won[1], C. Masaki[1,2,3], A. Senay[1,3], M. Sheehy[1,2,3], H. Patel[1,2,3] and T. Burke[1,2,4]

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Introduction: Lack of access to safe, affordable and timely anesthetic services, called the "anesthesia gap", is one of the primary barriers to universal surgical coverage. The purpose of this study was to describe a series of orthopedic procedures and operations supported by a novel package, designed for use when no anesthetist is available, called Every Second Matters for Emergency and Essential Surgery-Ketamine (ESM-Ketamine^{TM}).

Methods: The ESM-Ketamine™ package includes a defined clinical pathway, complemented by wall charts, checklists, and ESM-Ketamine kits, for use when no anesthetist is available. Mid-level and higher non-anesthetist providers underwent a 5-day training program on the ESM-Ketamine pathway. Data were prospectively collected for all cases in which the ESM-Ketamine pathway was utilized, and a sub-analysis performed on all patients that underwent orthopedic operative and painful procedures.
Results: Between December 2013 and March 2017, ESM-Ketamine providers from nine facilities in Kenya supported 345 orthopedic surgical procedures using the ESM-Ketamine package. Fifteen (4.3%) of the 345 were training cases and 330 (95.7%) supported by an ESM-Ketamine provider in the absence of a trained anesthetist. Prolonged (>30 seconds) oxygen desaturations below 92% occurred in 4 (1.2%) cases, brief (<30 seconds) oxygen desaturations in 12 (3.5%), hallucinations and/or agitation treated with diazepam in 49 (14.2%) and hypersalivation treated with atropine in 34 (9.9%). There were no post-recovery anesthesia related complications.
Conclusion: The ESM-Ketamine package appears able to help address the anesthesia gap crisis and thereby increase access to emergency and essential orthopedic surgical procedures when no anesthetist is available.

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Malissa Wood, MD, Medicine - Cardiology

Impella Mechanical Circulatory Support in Spontaneous Coronary Artery Dissection: Hemodynamic and Coronary Effects Using a Porcine Model

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Introduction: Spontaneous coronary artery dissection (SCAD) is an uncommon and under-diagnosed cause of acute coronary syndrome (ACS). Approximately 3-4% of all ACS patients and at least 30% of women less than 50 years of age with ACS are found to have SCAD. Risk factors include fibromuscular dysplasia, peripartum state and emotional or physical stress. After the index event, 15-20% of SCAD patients progress to heart failure. SCAD should be distinguished from atherosclerotic CAD as the management approach differs. Given the lower likelihood of technical success in SCAD with PCI and CABG, a conservative strategy is preferred in clinically stable patients; CTA and coronary angiography demonstrate near complete healing of most SCAD lesions within 3 months if patients survive the acute event. The appropriate mechanical circulatory support (MCS) approach to hemodynamically unstable SCAD patients has not been studied. Here we used a porcine model to investigate the hemodynamic and coronary effects of LV-Ao unloading with the Impella CP® (Abiomed, Danvers, MA) device in an LAD dissection model.
Methods: An Impella CP® was placed in the LV of two >70 kg Yorkshire pigs under fluoroscopic guidance. Pressure wires (PressureWire™ Aeris™ St Jude Medical™, St Paul, MN) measured aortic pressure (Pa) and coronary artery pressure distal to the dissection (Pd). Fractional flow reserve (FFR) in the LAD was calculated using the Pd/Pa ratio. Initially the Impella® was set at P0 (no forward flow). An iatrogenic dissection was created in the mid-LAD using the stiff end of an 0.018" guidewire and confirmed angiographically (Figure 1). The pump speed was increased to and maintained at 44000 rpm (P8) for 15-20 minutes. Angiograms and continuous FFR monitored the severity of the dissection as well as the coronary artery pressure.
Results: With Impella® use there was no angiographic evidence of dissection propagation. Additionally there was no physiologic evidence of worsening dissection as FFR remained constant. Diastolic coronary artery pressure increased while peak systolic pressure was unchanged (Table 1).
Conclusion: This experimental work suggests that using the Impella® CP in coronary artery dissections increases the diastolic coronary artery pressure and does not worsen the dissection. More work is needed to establish the safety profile of this approach in patients presenting with SCAD.

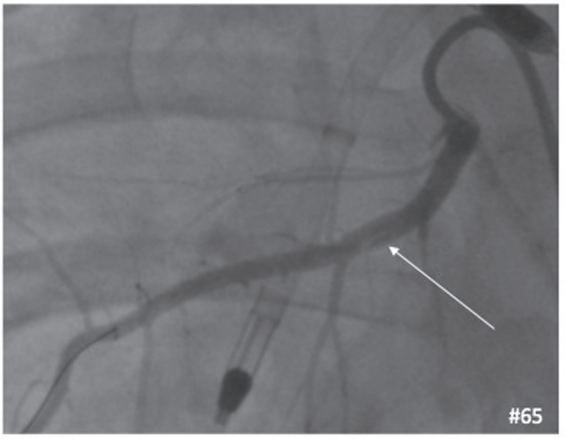

Figure 1. Sample angiographic image of iatrogenic LAD dissection created in Porcine Model 1

Table 1. Coronary Artery Pressure and FFR after iatrogenic LAD dissection and Impella support

	Porcine Model 1		Porcine Model 2	
Impella Speed	P0 (0 rpm)	P8 (44000 rpm)	P0 (0 rpm)	P8 (44000 rpm)
Pa (mmHg)	81/43 (60)	79/55 (66)	95/60 (76)	90/70 (79)
Pd (mmHg)	73/34 (50)	74/50 (60)	85/51 (66)	82/62 (68)
FFR	0.84	0.91	0.86	0.87

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Malissa J. Wood, Medicine - Cardiology

Clinical presentation, angiogram findings and management of Spontaneous Coronary Artery Dissection (SCAD) at Massachusetts General Hospital

M. Kaadan[1], S. Mishra[1], F. Ponzini[1], J.M. Duran[3], B. Ghoshhajra[2], M. Lindsay[4,5,6] and M.J. Wood[1]

[1]Cardiology, Massachusetts General Hospital, Boston, MA, USA, [2]Radiology, Massachusetts General Hospital, Boston, MA, USA, [3]Internal Medicine, Massachusetts General Hospital, Boston, MA, USA, [4]Thoracic Aortic Center, Massachusetts General Hospital, Boston, MA, USA, [5]Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA and [6]Cardiovascular Genetics Program, Massachusetts General Hospital, Boston, MA, USA

Introduction: Spontaneous Coronary Artery Dissection (SCAD) is an uncommonly diagnosed condition due to its similar presentation to atherosclerotic induced MI. Recent research has led to increased recognition of SCAD and associated conditions. As clinical awareness increases for SCAD, the causes are still relatively unclear. The purpose of this cross-sectional study is to analyze the clinical and angiographic features of the patients managed by the multidisciplinary program and Massachusetts General Hospital (MGH). The goal of our program is to provide an individualized approach to understand the triggers, associated conditions and develop a treatment plan for each patient in order to improve long term outcomes in these patients.

Methods: All patients seen in the multidisciplinary SCAD program at MGH who agreed to participated in the cross-sectional registry are included. Every patient involved in the study was given an individual study number, which de-identified all information to ensure confidentiality. The patients completed three questionnaires: demographics and social history, emotional state, and physical work capacity, which became part of their data for the study. Additionally, patient clinical history and angiogram data were collected via patients' charts, cardiovascular and abdominal imaging tests retrieved by the EPIC system.

Results: 114 patients, 86% female, mean ± SD age of 47±10.1 years were enrolled in the study. 29.5% of the patients reported a stressful event before SCAD whereas 42.9% were in rest during SCAD event. The most three common presenting symptoms were chest pain/discomfort, radiation to left arm, dyspnea (76.3%, 24.6%, 17.5% respectively). 29.7 % of the patients have high blood pressure as a risk factor. STAI1 and STAI2 mean ± SD 46.9±4.7 and 44.5±3.8 respectively. 54.4% had no ST elevation on their admission ECG, and 11.4% had cardiac arrest. Multivessel SCAD was found in 46.4%; dLAD, mLAD, OM1 are the most affected vessels (33.6%, 29.1%, 28.85% respectively), and 87.8% of the patients had vessel tortuosity. Two third of the patients were treated with medical management (66.67%) versus one third using stents (33.33%).

Conclusion: SCAD is prominently seen in females. HTN is the most common cardiac risk factor, and chest pain is the most reported symptom. More than half of the patients had no ST changes in their admission ECG.

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Malissa J. Wood, Medicine - Cardiology

Gender differences in the clinical presentation of Spontaneous Coronary Artery Dissection (SCAD) at Massachusetts General Hospital

M. Kaadan[1], F. Ponzini[1], S. Mishra[1], J.M. Duran[2], B. Ghoshhajra[3], M. Lindsay[4,5,6] and M.J. Wood[1]

[1]Cardiology, Massachusetts General Hospital, Boston, MA, USA, [2]Internal Medicine, Massachusetts General Hospital, Boston, MA, USA, [3]Radiology, Massachusetts General Hospital, Boston, MA, USA, [4]Thoracic Aortic Center, Massachusetts General Hospital, Boston, MA, USA, [5]Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA and [6]Cardiovascular Genetics Program, Massachusetts General Hospital, Boston, MA, USA

Introduction: Spontaneous Coronary Artery Dissection (SCAD) is a relatively rare type of Acute Coronary Syndrome (ACS). Recent research has shown that SCAD is more common in females. As SCAD clinical awareness increases, it continues to be under diagnosed in women due to its presentation as typical and atypical symptoms. This study investigates the gender differences in the clinical presentation of SCAD patients.
Methods: This is a cross sectional study of all patients with confirmed SCAD who were seen at the Massachusetts General Hospital (MGH) SCAD Program and enrolled in the MGH SCAD Registry. Our unique, multidisciplinary program provides a comprehensive and systematic approach to the evaluation of patients following SCAD. This approach includes cardiovascular, radiologic and genetic evaluations as appropriate. Upon enrollment, all patients completed a detailed questionnaire which collected demographic data and detailed health history including psychological, reproductive and general past medical history. Clinical history and imaging was abstracted from patient records and reviewed by study investigators.
Results: 114 patients were included in this study, there were 98 (86%) women and 16 (14%) men. The mean ± SD age was 47.4±9.5 years for women and 44.3±13.5 years for men (p=0.38). Men were more likely to experience SCAD while exercising (50% versus 15.6% of females), whereas women were more likely to experience SCAD while resting (42.9 % versus 25% of males) (p=0.01). Chest pain/discomfort is the most common symptom in both females and males (75.5% and 81.2% respectively) (p= 0.61**)**. STAI1 were significantly higher in men than women; STAI1 mean ± SD 48.9±3.4 for men and 46.6 ±4.8 for female (p=0.04). However, STAI2 mean ± SD, 44.9±3.2 for men and 44.4±3.9 for female (p=0.63). Prevalence of migraines (P=0.04), depression (P=0.04), and anxiety (P=0.01) were significantly higher in women than men (30.6% vs 6.2%, 20.41% vs 0%, 30.6% vs 0%) respectively. 54.4% of women presented with non-ST elevation myocardial infarction (NSTEMI) versus 50% in men, and the remaining 41.8% women presented with ST-elevation myocardial infarction (STEMI) (P=0.68). Regarding coronary angiography, multivessel SCAD was more common in women (49.5%) than men (26.7%) (p=0.1). Gender differences with respect to affected coronary artery were also noted. While the dLAD was most commonly affected in women (36.8%), mLAD was most commonly affected in men (26.7%) (p=0.2). Females are more likely to have SCAD type 2 (84.2%) compared to males who are more likely to have SCAD type 1 (60%) (P≤0.001). There is slight difference in SCAD management between male and female; women were more likely to be conservatively managed compared to men (67.3% vs 62.5%, respectively (p=0.7).
Conclusion: There is a statistical relationship between gender and SCAD onset, STAI1, past medical history, and SCAD type.

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Luke T. Wooster, B.S., Medicine - Cardiology

Hepcidin Dysregulation and Iron Deficiency Following Left Ventricular Assist Device Therapy

L.T. Wooster[1], C.S. Bailey[1], H.J. Barnes[1], M. Buswell[1], S. Kilmarx[1], K. Milley[1], J. Camuso[1], K. Stettner[1], S.S. Thomas[1], E.E. Coglianese[1], D. D'Alessandro[2], R. Malhotra[1] and G.D. Lewis[1]

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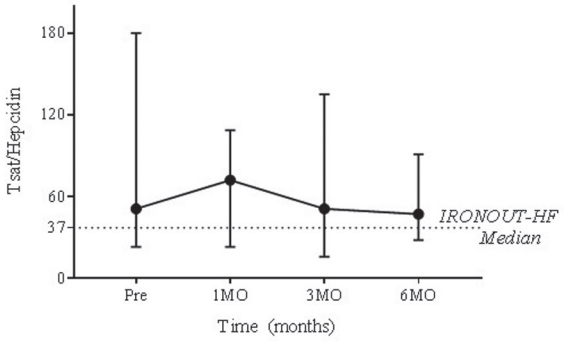
Introduction: Iron deficiency (IrDef) is present in ~50% of patients with heart failure (HF) and independently predicts functional impairment and adverse outcomes. Inappropriately elevated circulating hepcidin levels, thought to be driven by the pro-inflammatory state of HF, limit iron absorption and have recently been shown to predict refractoriness to oral iron repletion in HF. Whether hepcidin dysregulation persists following left ventricular assist device (LVADs) deployment to treat advanced HF is unknown.
Methods: Biorepository plasma samples and routine iron studies (iron, ferritin, total iron binding capacity) were collected in 27 patients pre-LVAD placement and at a 1, 3, and/or 6 month follow-up visits. Hepcidin levels were determined by DRG EIA-5258 ELISA and Tsat was derived from iron/TIBC.

Results: Prior to LVAD placement, 52% (n=14 of 27) were IrDef based on ferritin<100ng/ml or a Tsat <20% with ferritin<300ng/ml. The proportion of IrDef patients remained high (**Figure**) throughout follow-up. Hepcidin levels correlated with Tsat and ferritin levels (ρ =0.31 and 0.68, respectively, $p<0.05$ for both). However, at baseline and at each time-point post-LVAD Tsat/hepcidin ratios remained low and did not differ significantly from pre- to post-LVAD, with median values similar to those observed in the IRONOUT Trial (**Figure**).
Conclusion: Hepcidin levels are elevated in relation to the degree of IrDef pre- and post-LVAD placement in advanced HF. These findings suggest that intravenous iron, which circumvents hepcidin blockade of iron absorption, may be necessary to achieve iron repletion in HF patients post-LVAD.



Characteristic	Pre-LVAD	1 Month Post	3 Month Post	6 Month Post
N	27	20	22	19
Iron Deficient, %	52	80	55	63
Hepcidin, ng/ml	9.6 (3.9,25.6)	8.6 (1.9,22.7)	13 (3.7,25.2)	7.0 (4.7,24.8)
Tsat, %	16 (12,25)	11 (9,19)	20 (13,27)	19 (10,22)
Hepcidin/Tsat	51 (23,180)	72 (23,109)	51 (16,135)	47 (28,91)
Ferritin, ng/ml	151 (85,323)	112 (90,266)	99 (33,272)	85 (17,230)

Data presented as median (IQR)

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Emily Wright, Psychiatry

Timing and nature of discussions about hospice among patients with advanced cancer

E. Wright[1,2], A. El-Jawahri[1,2], J.S. Temel[1,2] and L. Traeger[1,3]

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Introduction: Timely and effective patient-clinician communication is considered essential to quality end-of-life (EOL) care, yet discussions about hospice often occur late in the course of disease. We examined the timing and nature of documented first discussions about hospice among patients with advanced cancer, their families, and clinicians.
Methods: We analyzed data from a randomized trial of early palliative care integrated with oncology care versus usual oncology care in patients with newly diagnosed incurable lung or non-colorectal gastrointestinal cancer at the Massachusetts General Hospital (n=350, enrolled 5/11-7/15). Our analysis included patients who were deceased at 1 year after the last enrollment (n=259). We reviewed electronic health records to identify the first documented hospice discussion with a medical oncology or palliative care clinician (date, location) and hospice enrollment (Y/N, date). Among hospice enrollees, we tested associations of first documented hospice discussion with location of discussion and subsequent hospice length of stay, adjusting for disease type (lung or GI) and randomized group. Among patients with a first documented discussion of hospice >30 days before hospice enrollment (n=66), we extracted the clinical documentation of this encounter and analyzed these notes qualitatively using content analysis.
Results: In this sample (54% male; 72.2% married/partnered; mean age=64.4 yrs [SD=10.6 yrs]), 79.9% (207/259) enrolled in hospice. Among hospice enrollees, 8.2% had no documented discussion about hospice before enrollment. Time from first documented discussion to hospice enrollment was ≤7 days (40.0%), 8-14 days (12.1%), 15-30 days (13.2%) or >30 days (34.7%). Among hospice enrollees, an earlier first documented discussion of hospice relative to hospice enrollment was independently associated with more days on hospice (Beta=.14, SE=.04, p<.001). Among patients who had their first discussion >30 days before hospice enrollment (n=66), notes for 46 patients (69.7%) documented the patient and/or family's point of view. Most patients felt unready and/or unwilling to consider transitioning to hospice and wished to continue treatment, though some wanted or were open to utilizing hospice in the future. Notes for 28 of these 66 patients with early first

hospice discussions (42.4%) documented a provider recommendation regarding pursuing or discontinuing chemotherapy, transitioning to hospice, and/or other EOL planning or care suggestions. The outcomes of these early hospice discussions were to continue treatment (n=15), continue discussions about EOL care (n=12), incorporate hospice into a future care plan (n=10), identify if/when scenarios for hospice (n=6), refer to hospice (n=6), or refer to bridge to hospice (n=3), and some outcomes were not documented clearly (n=14).
Conclusion: These findings suggest that engaging in earlier hospice discussions may improve EOL care delivery and facilitate patient-centered care with respect to when and how patients begin to discuss EOL care values and preferences. Research is needed to understand the longitudinal course of hospice discussions as well as the characteristics of patient-clinician communication about hospice that facilitate optimal EOL care.

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Huiliang Yang, MD, Orthopedics

Risk factors for the development of focal kyphosis and the effects on patients with spinal epidural abscess

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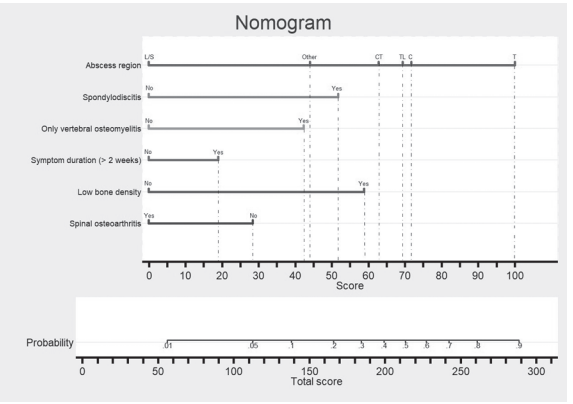
Introduction: While rare, spinal epidural abscess (SEA) is associated with significant morbidity and mortality. In addition to the potentially catastrophic neurologic deficits incurred from this disease process, SEA may also lead to bone destruction resulting in focal kyphosis of the affected spinal segments. Focal kyphosis can cause neurologic deficit and instability of the spine, resulting in the need for emergency spinal cord decompression and spine fixation. The incidence of spinal focal kyphosis and risk factors associated with its development are not well characterized in the literature.
Methods: We conducted a retrospective cohort study using electronic records in our hospital system. All patients were over 18 years old and had a clinically and radiologically documented SEA during the period 1993-2016. When prior spinal imaging was available, we identified obvious focal kyphosis by a change from the baseline radiological studies. When prior spinal imaging was not available, we identified the focal kyphosis through radiological reports and other electronic records. Meanwhile, Cobb angle change must be more than 5° (Cobb angle Change = middle Cobb angle – (superior Cobb angle + inferior Cobb angle)/2)). We analyzed the risk factors for the development of focal kyphosis through bivariate analysis and multivariate analysis. We made a nomogram to predict focal kyphosis. We analyzed the association of focal kyphosis with outcomes using univariate logistic regression.
Results: The study included 1,053 patients with SEA, 108 of whom developed obvious focal kyphosis. After stepwise multivariate logistic analysis, we eventually identified 1 protective factor and 5 risk factors for focal kyphosis. The protective factor was spinal osteoarthritis ($p=0.004$). Risk factors included low bone density in the past year ($p < 0.001$), symptom duration > 2 weeks ($p=0.024$), vertebral osteomyelitis ($p = 0.003$), spondylodiscitis ($p < 0.001$), and the involved region of the spine, in reference to the lumbar/sacral region (cervical, $p < 0.001$; cervicothoracic, $p = 0.004$; thoracic, $p < 0.001$; thoracolumbar, $p < 0.001$; multifocal/>2 contiguous regions, $p = 0.040$). The nomogram was made according to final multivariate logistic model. The final multivariable model was well calibrated ($p = 0.991$) and demonstrated good discriminatory ability, with an area under the curve (AUC) of 0.871. Bootstrap validation of the final model provided a bias-corrected AUC of 0.859. Through univariate logistic regression, focal kyphosis was significantly associated with motor deficit ($p<0.001$) at admission. Focal kyphosis was a risk factor for surgery ($p=0.001$), even instrumentation ($p<0.001$). In addition, focal kyphosis was significantly associated with residual motor deficit at last follow up ($p=0.002$) and failure of initial non-operative treatment ($p=0.003$). Focal kyphosis was not significantly associated with 90-day mortality or SEA recurrence.
Conclusion: In this cohort of patients, 10% developed focal kyphosis. The loss of bone density, cervical/thoracic SEA, longer symptom duration, and vertebral osteomyelitis were risks factor for the development of focal kyphosis. Low bone density and vertebral osteomyelitis can weaken the vertebrae, allowing them to be easily compressed. Long symptom duration provides pathogens enough time to erode vertebrae. Location in the cervical and thoracic spine could be a risk factor for focal kyphosis, as a result of the narrow spinal canal and natural kyphotic curve of the thoracic spine. However, osteoarthritis was a protective factor for focal kyphosis since it can strengthen the spine through osteophytes and inflammation. Focal kyphosis was significantly associated with patients' neurologic status at admission and residual motor deficit after treatment since focal kyphosis can worsen spinal cord compression and myelopathy. Moreover, focal kyphosis also increased the probability of receiving surgery and even new instrumentation for patients with SEA, as a result of vertebrae compression, spinal cord compression, and spine instability. Nomogram was friendly used for clinicians and patients to understand the probability of developing focal kyphosis in patients with SEA. Our study could help clinicians fully understand the development of focal kyphosis and its effects, thus preventing the development of focal kyphosis in patients with SEA by treating to increase bone density and using an orthosis brace.

Table 3. Multivariate analysis analyzing factors associated with severe focal kyphosis and the effects of focal kyphosis (n=1051)

Variables	Coefficient	OR	Standard error	p Value
Low Bone density	1.717	5.57 (3.33 to 9.33)	1.465	**<0.001**
Osteoarthritis	-0.829	0.44 (0.25 to 0.77)	0.126	**0.004**
Symptom duration prior to presentation >2 weeks	0.552	1.74 (1.08 to 2.80)	0.424	**0.024**
Vertebral osteomyelitis	1.236	3.44 (1.52 to 7.79)	1.435	**0.003**
Spondylodiscitis	1.512	4.53 (2.50 to 8.23)	1.379	**<0.001**
Involved region of spine				
Lumbar/sacral	Reference	Reference	Reference	Reference
Cervical	2.095	8.12 (3.53 to 18.67)	3.449	**<0.001**
Cervicothoracic	1.835	6.27 (1.79 to 21.90)	4.000	**0.004**
Thoracic	2.921	18.56 (9.21 to 37.38)	6.631	**<0.001**
Thoracolumbar	2.024	7.57 (2.83 to 20.27)	3.805	**<0.001**
Multifocal/>2 contiguous regions	1.285	3.61 (1.06 to 12.33)	2.263	**0.040**

Bold indicates significant difference (p<0.05).



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Elaine W. Yu, MD, MMSc, Medicine - Endocrine

Longitudinal 5-year changes in bone density and microarchitecture after Roux-En-Y Gastric Bypass

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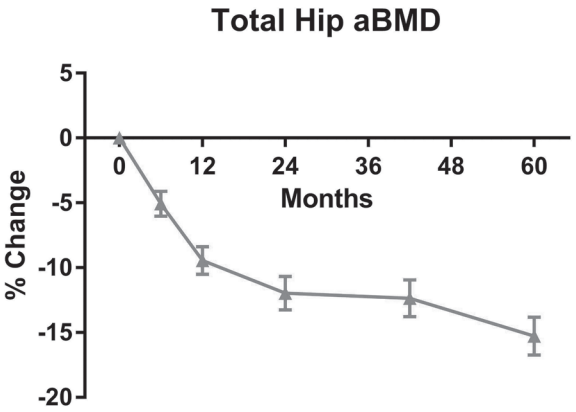
Introduction: Roux-en-Y Gastric Bypass (RYGB) leads to substantial postoperative bone loss, but it is unknown whether accelerated bone loss is sustained beyond 2 years. We characterized longitudinal changes in bone mineral density (BMD) and bone microarchitecture in the 5 years after RYGB.

Methods: We prospectively evaluated 21 adults (17F, 4M; mean age 51 ± 14 [SD] years) with severe obesity (BMI 45 ± 7 kg/m^2) who underwent RYGB in a 5-year longitudinal extension study. Areal BMD (aBMD) was measured at the lumbar spine, total hip, and 1/3 radius by dual-energy x-ray absorptiometry (DXA). Vertebral trabecular volumetric BMD (vBMD) at L1-L2 was measured by quantitative computed tomography (QCT). High-resolution peripheral QCT (HR-pQCT) was used to assess bone microarchitecture of the distal radius and tibia. We analyzed changes between 2 and 5 years using paired t-tests.

Results: Five years after RYGB, weight loss was 33 ± 12 kg, with stable weight between years 2 and 5. Cumulative declines in aBMD were -14.1 ± 8.0% at the total hip and -7.0 ± 10.6% at the 1/3 radius, with continued declines from 2 to 5 years ($p \leq 0.008$ for both). 5-year decrease in spine aBMD was -7.9 ± 7.6%, but did not differ from bone loss at 2 years. However, vertebral trabecular vBMD showed a cumulative decline of -12.1 ± 12.3%, which was significantly greater than bone loss at 2 years ($p=0.002$). 5-year declines in total vBMD were -18.7 ± 5.3% at the radius and -14.3 ± 5.0% at the tibia, and were due to decreases in cortical and trabecular vBMD that were greater than bone loss at 2 years ($p \leq 0.04$ for all). Between 2 and 5 years, there was continued deterioration in bone microarchitecture at the radius, with decreased cortical thickness and trabecular number, and increased trabecular separation ($p \leq 0.01$ for all). An attenuated pattern of microarchitectural decline was seen at the tibia, with no significant differences between 2 and 5 years. Serum calcium and 25(OH)VitD were unchanged from baseline after RYGB. There were no consistent associations between changes in aBMD or vBMD with loss of weight or lean mass.

Conclusion: Large cumulative declines in BMD and microarchitecture occur after RYGB, with continued worsening between years 2 and 5 at multiple skeletal sites, and in both cortical and trabecular bone. This persistent deterioration raises concerns about the long-term skeletal consequences of RYGB, and indicates that active management of bone health in these patients is warranted.

	% Change at 2 years (Mean ± SD)		% Change at 5 years (Mean ± SD)		p-value (2 years vs. 5 years)	
DXA (aBMD)						
Spine	-6.0 ± 6.5		-7.9 ± 7.6		0.09	
Total Hip	-12.0 ± 5.4		-15.3 ± 6.3		0.005	
1/3 Radius	-2.2 ± 9.5		-7.0 ± 10.6		0.008	
QCT (vBMD)						
Trabecular Spine	-7.6 ± 10.2		-12.1 ± 12.3		0.002	
HRpQCT	**Radius**	**Tibia**	**Radius**	**Tibia**	**Radius**	**Tibia**
Total vBMD	-7.4 ± 4.5	-7.7 ± 3.7	-18.7 ± 5.3	-14.3 ± 5.0	<0.001	<0.001
Cortical vBMD	-3.3 ± 3.3	-4.7 ± 3.0	-7.4 ± 5.7	-8.3 ± 5.5	0.02	0.04
Trabecular vBMD	-6.3 ± 3.9	-2.5 ± 4.2	-19.5 ± 9.1	-10.4 ± 12.1	<0.001	0.01
Cortical Thickness	-9.9 ± 7.5	-12.0 ± 8.6	-18.6 ± 10.7	-17.5 ± 13.9	0.01	0.18
Trabecular Thickness	-1.3 ± 10.0	2.2 ± 18.0	1.0 ± 10.7	-4.4 ± 16.7	0.66	0.33
Trabecular Number	-4.0 ± 11.1	-1.9 ± 17.0	-20.1 ± 10.6	-6.2 ± 13.8	0.004	0.21
Trabecular separation	6.6 ± 10.6	5.3 ± 18.8	31.8 ± 23.0	11.4 ± 18.8	0.01	0.15



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Amy Yule, Psychiatry

Risk Factors Associated with Overdose During Follow-up in Treatment-Seeking Youth with Substance Use Disorders

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Introduction: The main aims of this study were to identify the incidence of non-fatal and fatal overdose (OD) among youth engaged in outpatient substance use disorder (SUD) treatment, and to identify substance use and psychiatric characteristics associated with OD.
Methods: Systematic review of the medical records of patients ages 16 to 26 years of age, mean age 20.2 ± 2.8 years, who had a comprehensive semi-structured initial evaluation and engaged in care or had a fatal OD. Unintentional OD was defined as substance use without the intention of self-harm that was associated with significant impairment in level of consciousness. Intentional OD was defined as ingestion of a substance that was reported as a suicide attempt. Engagement in care was defined as two follow-up appointments within 30 days of the initial evaluation. T-tests, Pearson's chi-square, and Fisher's exact tests were performed to evaluate for substance use and mental health characteristics associated with OD.
Results: In all, 127 (64%) of 200 patients seen for an intake assessment engaged in care and 10 patients (8%) had a non-fatal OD within the subsequent 2.5 years. Ten independently collected patients had a fatal OD. There were no differences in substance use or mental health characteristics between the non-fatal and fatal OD groups (all $p \geq 0.05$) and the groups were therefore combined for analysis. Compared to those without OD those with an OD were more likely to have a lifetime history of opioid use disorder, cocaine use disorder, intravenous drug use, inpatient detoxification, mood disorder NOS, self-injurious behavior, or during follow-up to receive medication assisted treatment, SUD treatment in a different program, or be seen for psychopharmacology (all $p<0.05$).
Conclusion: Treatment-seeking youth with a SUD who had an OD during follow-up were more likely to have characteristics associated with a more severe SUD compared to patients with no history of OD.

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Alexander V. Zaitsev, Ph.D., Psychiatry

DL-XNAT: neurological experimentation system evolving on service oriented architecture and microservices paradigm

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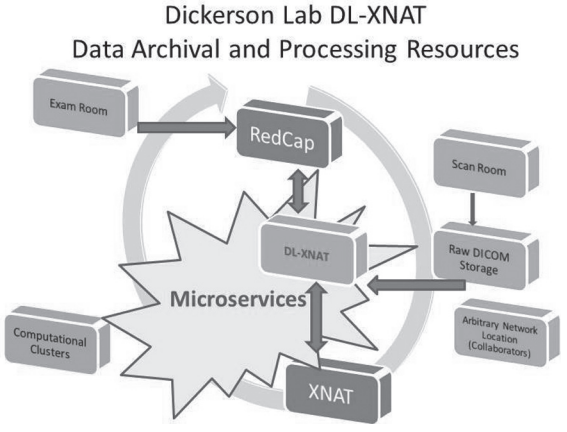
Introduction: Neuroimaging research teams face many organizational obstacles when dealing with large scale, multimodal datasets. Among these, some of the most difficult, recurring problems are image archive scalability, variations in image archiving pathways, non-uniform data tracking, structural changes of non-imaging data collection, computational complexity, image processing redundancy, and collaboration management. In Dickerson Lab (DL) we developed a solution tailored to overcoming these issues. Our system, DL-XNAT, used XNAT (eXtensible Neuroimaging Archive Toolkit, developed at

Washington University at St. Louis) as a foundation, and added many features to further streamline our data management. The most essential feature for the DL-XNAT project was the ability for remote, automated programmatical interaction with most XNAT modules via widely accepted and mature remote web communication and image exchange protocols: RESTful and DICOM listener respectively. Hence, XNAT was the first and fundamental module for the service oriented architecture (SOA) system we have built.

Methods: The nature of SOA allowed us to deploy the flexible distributed computational system (DL-XNAT) where new features are developed while existing features are actively used for research, receiving and being improved as needed iterative improvements based on user feedback. In addition to a SOA concept, where DL-XNAT webservices and GUI provide governed orchestration of data and processing flow between distributed modules, DL-XNAT utilizes the emerging concept of microservices. Microsrvices differ from the traditional comprehensive web services and complex applications in the following ways: the microservices represent distributed lightweight and highly specialized applications that can be deployed at various locations. The functionality and location depend on the tasks that have to be performed by a given microservice. Such tasks can include, for example, checking for new MRI sessions' arrival, anonymization and forwarding images to XNAT archive, downloading series of interest from XNAT and dispatching them to the processing at High Performance Computation Clusters (HPCC). Usually, the microservices are governed by the complex dispatch system, which may have no direct access to the microservices' locations. The presented DL-XNAT is that system. For example, such microservices verify of XNAT's DICOM listener's files' upload integrity, dispatch the images to the pipeline processing at HPCC, and notify the user about image processing submission, completion or termination.

Results: Starting with the legacy image collection consolidation via controlled bulk uploading from network storage location to XNAT, the DL-XNAT represents a multifunctional neuroscience projects support system, where each step of the image archiving and processing live-cycle is being tracked, dispatched, and quality controlled. The current features of DL-XNAT provide the following: semi-automated image uploads from in-house MRI facilities as well as external (collaboration) sources DICOM upload integrity control problem reporting, such as incomplete uploads, duplicates, image origin DICOM paths conflicts, etc. QC annotation for image sessions and individual series clinical and other non-imaging data storage on RedCap (the RedCap's RESTful API allows a similar remote interaction as with XNAT) search engine based on clinical, image series and QC note parameters image processing submission and monitoring at HPCC tracking the image processing outputs as well as storing parameters used during processing

Conclusion: These features allow us to streamline image archiving, keep archived images as a protected immutable collection with direct access by a limited number of privileged users (most interactions with XNAT, RedCap and other entities are done with the DL-XNAT Web Interface), provide participating researchers with clean image sets, and leverage image processing while preventing inter-project processing redundancy. The hybrid SOA and microservices approach allowed not only gradual deployment and independent development of new modules and features, but also made participation of non-programmers, such as prospective users and subject experts more effective and less time consuming. Thanks to the microservices deployment and update agility, some of the features could be added and/or improved in a matter of hours. The protocols of communication between web pages and microservices allowed us to deploy rich GUI web pages. Most of DL-XNAT web pages consist of multiple components that interact with XNAT, RedCap and distributed microservices independently and asynchronously (AJAX/JavaScript technology). That provides end users with the web GUI acting as responsive desktop applications without the need pages reload and/or redirection. The examples of real cases image archiving and processing lifecycle will be presented on the poster.



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Jonathan P. Zebrowski, Psychiatry

Longitudinal evolution of sleep dysfunction during first year of residency

J.P. Zebrowski[1,2], S.J. Pulliam[3], J.W. Denninger[1] and L.R. Berkowitz[4,5]

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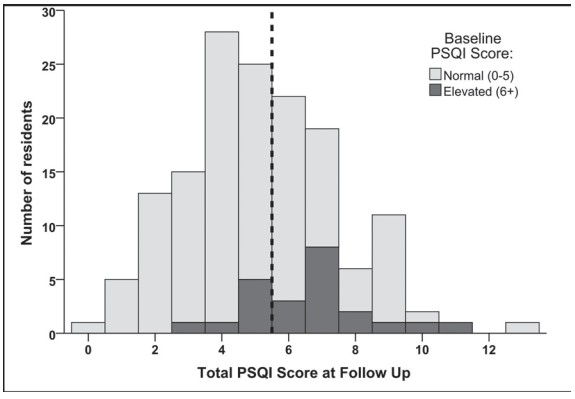
Introduction: Restrictions on work hours for medical residents have been proposed as helpful for improving sleep, resident health and patient safety and continue to be debated. Few studies have tracked sleep dysfunction longitudinally during residency to establish effects of changing work hour rules.

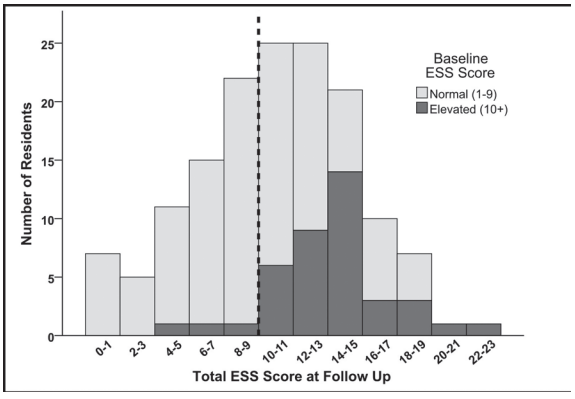
Methods: Voluntary surveys were administered to first-year residents at Massachusetts General Hospital and Brigham and Women's Hospital at two time points: at orientation prior to beginning clinical work and at a retreat for first-year residents held approximately nine months into training. Data was gathered in 2011-2012; this was the first academic year of more stringent rules on intern work hours, including maximum shift duration of 16 hours. Surveys included demographic information and two validated questionnaires assessing sleep dysfunction: the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS).

Results: 281 residents completed the initial survey, and 153 (54%) completed matched surveys at follow-up. There were no significant differences in demographics or baseline PSQI and ESS scores between residents who completed a follow up survey and those who did not. Mean nightly sleep time decreased from 7.6 hours initially to 6.5 hours at follow-up ($p < .001$). Mean PSQI score increased from 3.6 to 5.2 ($p < .001$); a PSQI score of 6 or above indicates dysfunctional sleep. Mean ESS score increased from 7.2 to 10.4 ($p < .001$); an ESS score of 10 or above indicates excessive daytime sleepiness. In a linear regression to identify demographic predictors of sleep disturbance, greater age was a significant predictor of higher PSQI score ($p < .01$) but not ESS score. Other demographic variables (gender, surgical vs. non-surgical specialty, number of children) were not significant predictors.

Conclusion: Despite work hour restrictions, duration of sleep, quality of sleep and excessive daytime sleepiness worsened over the course of the first year of residency compared to baseline. Efforts should be undertaken to understand factors other than work hours that contribute to dysfunctional sleep in residency trainees in an effort to enhance resident health.



Residents with elevated scores on the PSQI tended to remain in the elevated score group at follow up. The cutoff value corresponding to poor sleep quality is indicated by the dashed line.



Residents with elevated scores on the ESS tended to remain in the elevated score group at follow up. The cutoff value corresponding to excessive daytime sleepiness is indicated by the dashed line.

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Mingjuan L. Zhang, MD, Pathology

Differential Expression of Immune Inhibitory Markers in Association with the Immune Microenvironment in Resected Lung Adenocarcinomas

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Introduction: Similar to programed death ligand 1 (PD-L1), indoleamine 2,3-Dioxygenase 1 (IDO1) has been shown to exert potent immunosuppressive effects and be variably expressed in human lung cancer. However, IDO1 expression has not been well studied in lung adenocarcinoma (ADC).
Methods: PD-L1 and IDO1 expression were evaluated in 261 resected ADC using tissue microarrays and H-scores (cutoff: 5). We compared IDO1 with PD-L1 expression in association with clinicopathologic features including subtypes of tumor-infiltrating lymphocytes (TILs), HLA class I (beta-2 microglobulin; B2M) expression, molecular alterations and patient outcomes.
Results: There was expression of PD-L1 in 89 (34.1%) and IDO1 in 74 (28.5%) cases, with co-expression present in 49 (18.8%). Both PD-L1 and IDO1 expression were significantly associated with smoking history, aggressive pathologic features, and abundant CD8+ and T-bet+ (a marker for Th1 pathway) TILs. PD-L1 expression and abundant CD8+ were inversely associated with a loss of B2M membranous expression ($p=0.002$ and $p<0.001$, respectively). In cases with isolated IDO1 expression, abundant CD8+ and T-bet+ TILs were present in 0% and 8.0%, significantly fewer than PD-L1+/IDO1+ and PD-L1+ only cases ($p<0.001$, respectively). PD-L1 expression was significantly associated with *EGFR* wild-type ($p<0.001$) and *KRAS* mutants ($p=0.021$). However, there was no difference in IDO1 expression, in particular isolated IDO1 expression, between different molecular alterations. As for survival, PD-L1 expression was significantly associated with decreased progression-free (PFS) and overall survival (OS) by multivariate analyses, while IDO1 expression was associated only with decreased OS. Interestingly, there was a significant difference in the 5-year PFS and OS ($p=0.004$ and 0.038, respectively), where cases without PD-L1 or IDO1 expression had the longest survival, and those with PD-L1 expression only had the shortest survival.
Conclusion: While PD-L1 +/- IDO1 expression is observed in association with B2M expression, CTL/Th1 microenvironments, *EGFR* wild-type, and *KRAS* mutations, isolated IDO1 expression does not demonstrate these associations, suggesting that IDO1 may serve a distinct immunosuppressive role in ADC. Thus, blockade of IDO1 may represent an alternative and/or complementary therapeutic strategy to reactivate anti-tumor immunity.

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Ren Z. Zhang, MPH, Center for Human Genetic Research (CHGR)

Clinical Trial of L-Carnitine and Valproic Acid (CARNI-VAL) in Spinal Muscular Atrophy Type I

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Introduction: In spite of recent advances in the care of individuals with spinal muscular atrophy (SMA), SMA remains a leading cause of hereditary morbidity and mortality in infants and children. The specific aims of this open-label phase 2 multicenter trial of L-carnitine and VPA were to assess safety and adverse events in infants with SMA type I; to assess survival and time to death or need for > 16 hours ventilator support per day with post hoc matching to an untreated disease cohort; and to assess feasibility for recruitment and retention of symptomatic SMA type I infants in a multicenter clinical trial setting.

Methods: The SMA Type I CARNI-VAL trial was a multi-center open label phase 2 trial of L-carnitine and VPA in infants with SMA type I, aged 2 weeks to 12 months (Clinicaltrials.gov ID NCT00661453). We prospectively enrolled 37 infants with SMA type I between the ages of 2 weeks and 12 months of age at 8 centers. An untreated, matched disease cohort of 57 type I infants was selected retrospectively as a comparison group from a larger cohort of 151 SMA type I infants from the Project Cure SMA database, enrolled at the University of Utah under IRB protocol "Clinical and Genetic studies of SMA" between 2000 and 2015. Adverse event data was collected systematically throughout in accordance with Common Terminology Criteria for Adverse Event grading. Survival and outcome analyses between groups were described using Kaplan-Meier curves. TIMPSI data and CMAP NPamp data were used to measure motor function and as a surrogate to assess denervation. TIMPSI total score and CMAP NPamp changes from baseline to 3 and 6 month visits were examined within the CARNI-VAL cohort using Wilcoxon SR tests or paired t-tests, depending on normality of distributions.

Results: Fifty-five subjects were screened to enroll 39 subjects across the 8 sites over a period of 21 months. Two subjects immediately withdrew due to illness leaving 37 subjects at intervention start. Twenty-two subjects (59%) did not complete the study: 14 died, 5 withdrew due to a serious adverse event (SAE), 1 had an inter-current illness, 1 withdrew due to surgery, and 1 withdrew for other reasons. Fifteen subjects (41%) completed all study visits. The known severity of disease burden and events associated with SMA type I contributed to the attrition rate. There were 245 AEs affecting 35 (95%) CARNI-VAL subjects, and 33 subjects (89%) had 1 or more SAEs, inclusive of severe adverse events, life-threatening adverse events, or death (Table 1). Fourteen infants (38%) died and 6 (16%) required > 16 hours of ventilation per day by study's end. Survival probabilities including survival or time to need for ventilation > 16 hours per day did not significantly differ between the CARNI-VAL and comparison groups (Figure 1).

Conclusion: In this open-label study, the prevalence of adverse events, many severe, in the CARNI-VAL treated cohort was highest in the categories of respiratory distress, respiratory infection and bulbar complications, consistent with known frequency, type and severity of events seen in the SMA type I population. Retention over one year was greater than 40%, despite an expected high attrition related to death and adverse events, providing support for feasibility of trials in infants with SMA type I. Treatment with L-carnitine and VPA in symptomatic infants with SMA type I had no significant impact on either survival or the combined endpoint of time to death and/or ventilator dependence >16 hours when compared to a natural history, matched disease cohort. Within the CARNI-VAL cohort, TIMPSI and ulnar CMAP testing suggested no consistent improvement in motor function or evident reinnervation. Given the medical fragility of these infants, the importance of special efforts to retain and support infants and their families is clearly evident. Guidelines for nutritional and respiratory support, therapies, acute care management, psychosocial support and access to palliative care resources should be applied consistently across centers in order to avoid confounding effects on outcomes. Pre-symptomatic diagnosis or efficient enrollment closely following the initial diagnosis is clearly preferable in order to maximize therapeutic benefit and minimize adverse outcomes. Finally, it is evident that the best chance for demonstrating therapeutic benefit for promising new therapies is to identify and enroll subjects as early as possible in the clinical course, ideally in the newborn period.

Adverse Events

CATEGORY of EVENT	ADVERSE EVENT		SERIOUS ADVERSE EVENT		DEATH		TOTAL EVENTS	TOTAL SUBJECTS
	Subjects N* (%)	Events	Subjects N* (%)	Events	Subjects N* (%)	Events		N (%)
Respiratory Infection	19 (51.3)	43	17 (45.9)	26	3 (8.1)	3	72	25 (67.6)
Respiratory Distress	7 (18.9)	8	14 (37.8)	32	8 (21.6)	8	48	22 (59.5)
Bulbar Insufficiency	8 (21.6)	10	18 (48.6)	25	1 (2.7)	1	36	22 (59.5)
Infectious, Other	17 (45.9)	31	3 (8.1)	3	0 (0)	0	34	17 (45.9)
Other/unspecified	12 (32.4)	16	9 (24.3)	10	2 (5.4)	2	28	18 (48.6)
Skin/Subcutaneous Tissue disorders	6 (16.2)	10	0 (0)	0	0 (0)	0	10	6 (16.2)
Reflux/Vomiting	4(10.8)	4	1 (2.7)	1	0 (0)	0	5	5 (13.5)
Diarrhea/ Constipation	3(8.1)	4	0 (0)	0	0 (0)	0	4	4 (10.8)
Cardiac	2 (5.4)	2	1 (2.7)	1	0 (0)	0	4	3 (8.1)
Neurologic	4 (10.8)	4	0 (0)	0	0 (0)	0	4	4 (10.8)
Total events	28 (75.7)	132	29 (78.4)	99	14 (37.8)	14	245	35 (94.6)

*N = 37 subjects

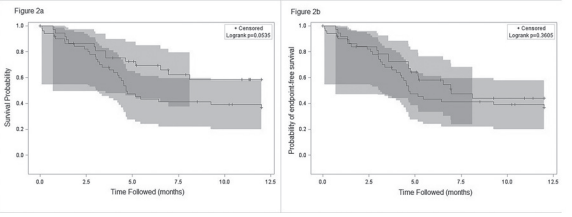

Figure 1. Survival probability for type I CARNI-VAL treated (blue) versus untreated (red) cohorts. Shaded areas represent 95% confidence intervals. 2a is time to death; 2b is combined endpoint of time to death and/or ventilator support > 16 hours.

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Surgical Decision Making in Median Neuropathy Associated With Distal Radius Fractures

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Introduction: A lack of conclusive evidence on the treatment of Acute Carpal Tunnel Syndrome (ACTS) in patients with distal radius fractures has led to inconsistent surgical guidelines and recommendations regarding ACTS in distal radius fractures. There is a wide variation in surgical decision making. We aimed to evaluate international differences between surgical considerations and practices related to carpal tunnel release (CTR) in the setting of distal radius fractures. We tested the primary null hypothesis that there are no differences in the risk assessment of fracture displacement on the development of ACTS in patients with a distal radius fracture between trauma surgeons from the Netherlands and trauma surgeons from the USA.

Methods: We approached surgeons who were a member of the Orthopaedic Trauma Association (USA) or of the Dutch Trauma Society (the Netherlands) and asked them to provide sociodemographic information and information on their surgical practice regarding carpal tunnel release in the setting of distal radius fractures. After applying our exclusion criteria, our final cohort consisted of 127 respondents (Table 1). We presented categorical data as frequencies with percentages and continuous data as means with their standard deviations. The demographic differences, differences in surgical practice and risk assessment, and differences in surgical decision making regarding CTR in the setting of distal radius fractures were all assessed through bivariate analysis.

Results: Compared to Dutch surgeons, surgeons from the USA are more of the opinion that displaced distal radius fractures are at risk of developing ACTS ($P < 0.001$) and consider persistent paresthesia in the median nerve distribution after closed reduction to be a surgical emergency less often ($P = 0.007$; table 2). Based on the mean summative scores that were assigned to the surgeon's decision making, surgeons from the USA are more likely to perform a CTR at the same time as distal radius ORIF (mean: 1.8 (SD 1.6), range: -3 to 6) when compared to surgeons from the Netherlands (mean: 0.96 (SD 2.4), range: -6 to 4; $P = 0.044$).

Conclusion: A lack of conclusive evidence has led to international differences in surgical practice regarding the treatment of ACTS in the setting of distal radius fractures. Future research should guide surgeons in making appropriate evidence-based decisions when performing CTR in the setting of distal radius fractures.

Table 1: Characteristics of the participating surgeons

Characteristic	All surgeons (n=127)	Dutch surgeons (n=26)	US surgeons (n=101)	P-value
Age, mean ± SD, years	50 ± 11	46 ± 7.9	52 ± 11	0.0091
Male sex, n (%)	117 (92)	23 (88)	94 (93)	0.43
Residency in same country as medical practice, n (%)	124 (98)	25 (96)	99 (98)	0.50
Work status, n (%)				>0.99
Full time	118 (93)	24 (92)	94 (93)	
Part time	5 (3.9	1 (3.9)	4 (4.0)	
Retired	4 (3.2)	1 (3.9)	3 (3.0)	
Position, n (%)				0.57
Surgeon	125 (98)	25 (96)	100 (99)	
Fellow	1 (0.79)	0 (0.0)	1 (0.99)	
Other	1 (0.79)	1 (3.9)	0 (0.0)	
Supervising surgeon, n (%)	87 (69)	22 (85)	65 (64)	0.059
Specialty, n (%)				<0.001
General Orthopaedic Surgery	9 (7.1)	0 (0.0)	9 (8.9)	
Orthopaedic Traumatology	45 (35)	23 (88)	22 (22)	
Hand and Wrist Surgery	73 (57)	3 (12)	70 (69)	
Years in practice since board certification, mean ± SD, years	16 ± 11	11 ± 7.5	18 ± 11	0.0033

Table 2: Differences in surgical practice and risk assessment regarding carpal tunnel release in the setting of distal radius fractures between surgeons from the Netherlands and surgeons from the USA.

Variable, n (%)	Country of surgical practice		P-value
	Netherlands (n=26)	USA (n=101)	
Surgical practice			
Performed elective open CTR in patients with CTS as part of his/her practice	13 (50)	81 (80)	0.005
Released a carpal tunnel, for any reason, in the past 4 weeks	12 (46)	76 (75)	0.008
Working in practice where ORIF of DRFx is a day surgery procedure	20 (77)	99 (98)	0.001
Has ever treated a patient with a displaced DRFx who also developed preoperative acute CTS	22 (85)	99 (98)	0.016
Has ever treated a patient with a displaced DRFx who also developed postoperative acute CTS	16 (62)	76 (75)	0.22
Has (institutional) clinical or radiographic guidelines to determine which DRFx are at risk of CTS	0 (0.0)	8 (7.9)	0.21
Performs routinely (>50% of the time) CTR at the same time as distal radius ORIF	1 (3.9)	9 (8.9)	0.69
Has ever returned to the operating room with a patient after distal radius ORIF for subsequent CTR	11 (42)	64 (63)	0.073
Changes the post-op rehabilitation if there was concurrent CTR during ORIF of the distal radius	2 (7.7)	11 (11)	>0.99
Routinely allows for preoperative peripheral nerve block placement for DRFx requiring surgery	15 (58)	73 (72)	0.16
Risk factor assessment:			
Believes that displaced DRFx are at risk of acute CTS	20 (77)	100 (99)	<0.001
Considers persistent paresthesia in the median nerve distribution after closed reduction of DRFx to be a surgical emergency	13 (50)	22 (22)	0.007

CTR: carpal tunnel release; CTS: carpal tunnel syndrome; DRFx: distal radius fracture; ORIF: open reduction internal fixation

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