Thank you for joining the webinar!
We are admitting audience members from the waiting room.
Please allow a few moments for the webinar to begin.
Biomarkers and ALL ALS
Clinical Research Consortium

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Sources of Biomarkers

- **Genetic**: Gene mutations or repeat expansions; Risk factors; Gene expression or splicing alterations
- **Biofluid**: CSF, Blood, Urine, Saliva
- **Tissue**: Muscle, Skin, Post-mortem tissues
- **Digital**: Speech, Movement
- **Imaging**: PET, MRI, DTI
Goals for Biomarkers in ALS Drug Development

Develop a “Biomarker Tool Kit” to help inform and make decisions in all steps of the drug development process.

- ALS Relevant & Druggable: Supported by genetics or -omics data
- Pre-clinical testing:
  - hits target
  - modulates pathway
  - Safety profile
  - PD biomarker
- Use in Human Studies:
  - Participant Selection
  - Target Engagement
  - Pharmacodynamics
- Enrollment in Studies:
  - Preclinical/Prodromal
  - Patient Stratification
  - Fast vs. Slow
- Accelerate Trials:
  - Well powered
  - Reduced time
  - Outcome measures
Fluid-based biomarkers to monitor ALS disease progression and/or treatment response

- Axonal injury/transport: Neurofilament (NF-L and pNFH); pTau181
- Inflammation: Chitinase proteins (YKL-40, Chit-1); MCP-1; CRP
- miRNAs: miR206; miR181; miR218; miR3911
- PBMC gene expression profile for IL-6 signaling
- Loss of TDP-43 function: Cryptic exon containing proteins (STMN2, UNC13A, HDGFL2)
- Protein aggregation/Autophagy/er stress: TDP-43; ATF4, CHAC1, TRIB3
- C9 related disease: Dipeptide repeat proteins (DPRs)
- Muscle related: Creatine kinase; Creatinine
Neurofilament is the Top Protein Biomarker for ALS and FTD
NFL as a Prognostic Biomarker

Biofluid levels correlate to rate of disease progression

Increases before symptom onset in asymptomatic gene carriers

Log-rank (Mantel-Cox) test:
Chi square: 34.83
p<0.0001

Tertile cutoff levels:
Cohort-specific

Percent survival

Time to event from baseline (months)

Lowest third
Middle third
Highest third

Amyotrophic Lateral Sclerosis and fronotemporal Degeneration, 2019; 20: 538–548

ANN NEUROL 2016;79:152–158
NFL as a Response to Drug Treatment

Decreased NFL in response to SOD1 ASO treatment

Increased NFL in response to C9 ASO treatment

Q’s:  What % change indicates impact on target pathway?  What % change correlates with positive clinical outcome measures?

N Engl J Med 2022; 387:1099-1110

Courtesy of Biogen and Ionis
Mass spectrometry proteomics of CSF identified significant global variations in the proteome that distinguished fast and slow progressors.
A mathematical model was generated that can predict who is a fast or slow progressor using mass spectrometry proteomics of a single CSF sample.
Urgent Need for Continued Research on ALS Biomarkers

Requires continued participation and collection of biosamples for research purposes

Currently enrolling ALS clinical research studies:
- Target ALS
- Natural History Study
- ALS-TDI
- CDC Registry and Biorepository
- Everything ALS
- DIALS, preFALS, PREVENT (Asymptomatic gene carriers)
Access for ALL with ALS Consortium

Funding started Oct 2023 by NINDS using ACT for ALS funds

Goals:

• Create a large, flexible ALS Research Consortium platform that can grow and be modified
• Provide opportunities for all individuals living with ALS in the United States to participate
• Run longitudinal natural history and biomarker studies
• Build a large openly shared data knowledge portal and biobank
• Provide clinical data and biosamples to better characterize ALS, identify biomarkers, and aid drug development
• Expand our goals to contribute ever more!
ACT for ALS Public-Private Partnership

AMP ALS
Goal: Accumulate Data and Facilitate Open Science

ALL ALS Consortium
Goal: Establish ALS consortium to run studies and collect prospective data

19 Sites
Barrow Neurological Institute

15 Sites
Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

Data Portal

Biorepository

Shared Protocols
OSMB
Steering Committee
Site Monitoring (BNI)

Shared DCC (MGH)
Single IRB (MGB)
34 Clinical Sites

WEST
- Barrow Neurological Institute
- Columbia University
- Washington University
- Georgetown University
- University of Washington
- University of California, San Diego
- Northwestern University
- Mayo Clinic
- Massachusetts General Hospital
- University of Colorado Denver
- Ohio State University
- Universidad de Puerto Rico
- Saint Alphonsus Regional Medical
- Henry Ford Health
- University of Michigan
- University of Minnesota
- University of California, Irvine
- Providence Brain and Spine
- University of Utah

EAST
- Texas Neurology
- Virginia Commonwealth University
- Temple University
- Pennsylvania State Medical Center
- Duke University
- Dartmouth Hitchcock
- University of Nebraska Medicine ALS Center
- Our Lady of the Lake Regional Medical Center
- Indiana University ALS Center
- Emory University
- Hospital for Special Care
- University of California, San Francisco
- University of Alabama, Birmingham
- Johns Hopkins University
- Houston Methodist
ALL ALS Enrollment Objectives

Enroll >2000 participants quickly!

Think Large and Inclusive
- Geography
- Race/ethnicity
- Socio-economic status
- Education level

Reduce Barriers to Participation
- Engage Study Sites
- Learn from People Living with ALS

Coordinate with ongoing studies
- Target ALS
- Natural History study
- PREVENT ALS

Outreach activities & communication
- ALS Association, MDA
- IAMALS, Everything ALS, etc.
- Community engagement science
Decentralized Study Methodology

Interest from Potential Participants
• Dedicated ALL ALS Website
• Recruitment Materials
• Community Engagement

E-Consent
• Use of electronic consent obtained remotely or onsite using secure web-based portal and devices

Data and Sample Collection
• Videoconference visits
• Patient-reported Outcomes collected using NeuroPRO
• Speech Recordings collected with Smartphone/Tablet App

Blood Collection Methods for different cohorts
• Option 1: Collect on-site at Clinics
• Option 2: Home phlebotomy
  • Requires phlebotomist and centrifuge in home (expensive)
  • Most convenient for off-site participants
  • May not reach all areas throughout the US
• Option 3: Blood Capillary Collection (YourBio)
  • Collects a small amount of blood (500uL)
  • Possible when Options 1 & 2 are not
Two Initial Study Protocols in ALL ALS:

1) ASSESS ALL ALS
2) PREVENT ALL ALS

Disclaimer: Both protocols and ICFs are under review by the sIRB and therefore may change based upon input from the IRB
ASSESS ALL ALS - STUDY DESIGN

ASSESS ALL ALS is a prospective, observational study enrolling individuals symptomatic for ALS and controls. Visits occur over 2 years duration may be on site or fully remote.

This is a longitudinal observational study involving collection of clinical data, outcome measures, speech and biofluid samples.

- Clinical Outcomes
- ePROs
- Cognitive Testing: ECAS
- Blood (CSF optional)
PREVENT ALL ALS is a prospective, observational cohort study enrolling individuals at risk for carrying inherited genetic variants known to be causative for ALS.

This is a longitudinal observational study to characterize asymptomatic ALS/FTD disease states by obtaining natural history data and performing longitudinal follow-up in people genetically at risk for ALS/FTD to collect clinical data, outcomes and biofluid samples.

Clinical Outcomes
- ePROs

Cognitive Testing:
- ECAS + FTLD-CDR
- CSF, Blood
Conclusions

• Tremendous progress on ALS biomarkers in the past decade
• Biomarkers are making significant impact on ALS drug development
• Participation in ALS clinical research studies is necessary to continue development of ALS biomarkers
• ALL ALS will hopefully enroll its first participants at the end of the summer

Happy to Answer any Questions