Study EAP04 | CNM-Au8 30 mg

ACT EAP Interim NfL Analyses Results

NIH Funded Expanded Access Programs (EAPs)

Sponsor	Study	Investigational Product	Type	Description
NINDS/Clene Nanomedicine	EAP	CNM-Au8	EAP	Energetic intervention
NINDS/Prilenia	EAP	Pridopidine	EAP	Sigma-1 receptor agonist
NINDS/ RAPA Therapeutics	EAP	RAPA-501	EAP	Autologous cell therapy to reduce neuroinflammation
NINDS/ Medicinova	EAP	Ibudilast	EAP	Phosphodiesterase inhibitor

NYU Langone Health

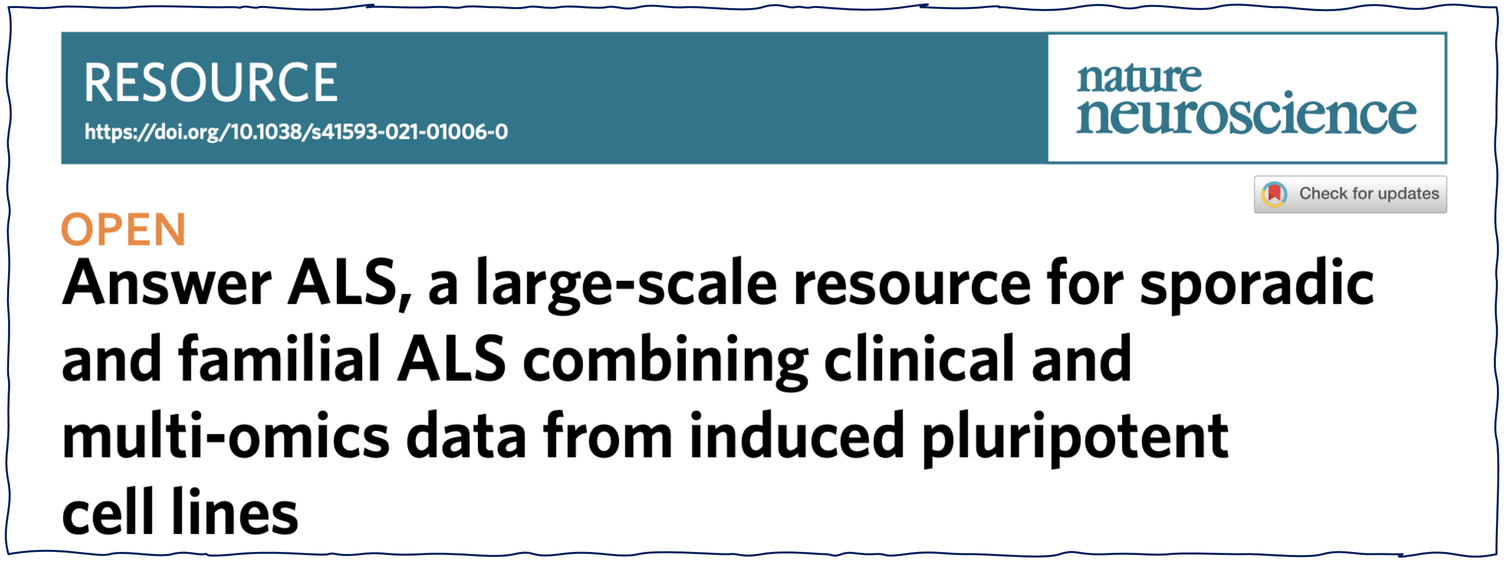
Intermediate-sized Expanded Access Protocol (EAP) for CNM-Au8 in Amyotrophic Lateral Sclerosis (ALS): Study Aims

Enrollment: Goal of up to 230 pwALS from across all 50 states in the US via virtual and in clinic enrollment	Partnership between academia, industry (Clene), and virtual site (Synapticure) Expanded enrollment (originally up to 100) due to high interest without change in scope or budget
Primary aim:	To evaluate the safety and efficacy of CNM-Au8 in non-clinical trial eligible pwALS
Exploratory aims:	Measure exploratory clinical outcomes (e.g. QoL, FSS, in addition to breathing, ALSFRS, and Survival) Evaluate candidate biomarkers (e.g. NfL, UCHL, serum creatine, metabolomic profiles, and others) Employ prediction algorithms tools to predict outcomes Feasibility of remote enrollment and participation

Comparator | EAP04 Propensity Matched to ANSWER ALS Controls

Prespecified Baseline Covariates for Matching

- NfL
- Age
- Sex
- Bulbar Onset Flag
- Riluzole Background Treatment
- Months from Symptom Onset
- delta FS (Pre-Treatment ALSFRS-R Slope)



RESOURCE

https://doi.org/10.1038/s41593-021-01006-0

nature neuroscience

Check for updates

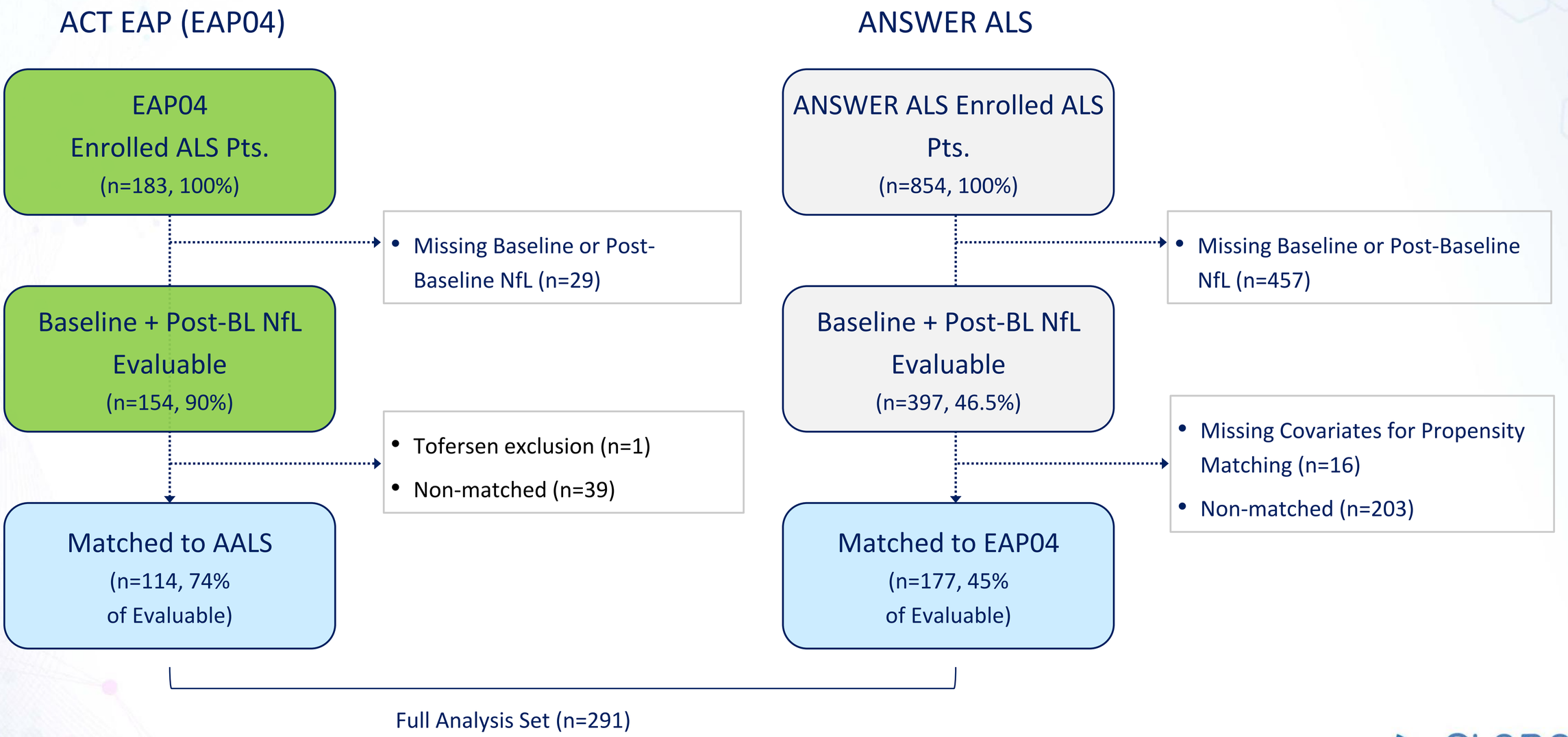
OPEN

Answer ALS, a large-scale resource for sporadic and familial ALS combining clinical and multi-omics data from induced pluripotent cell lines

Source: Baxi et al. Nature Neuroscience, Vol 25, February 2022, p. 226–237.

EAP04 Interim NfL Analyses | Full Analysis Set

AALS Matched Controls | Participant Flow

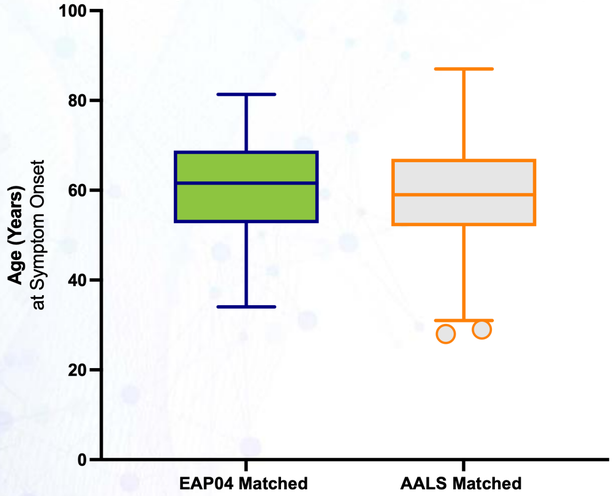


Data on File, Clene Nanomedicine, Inc.

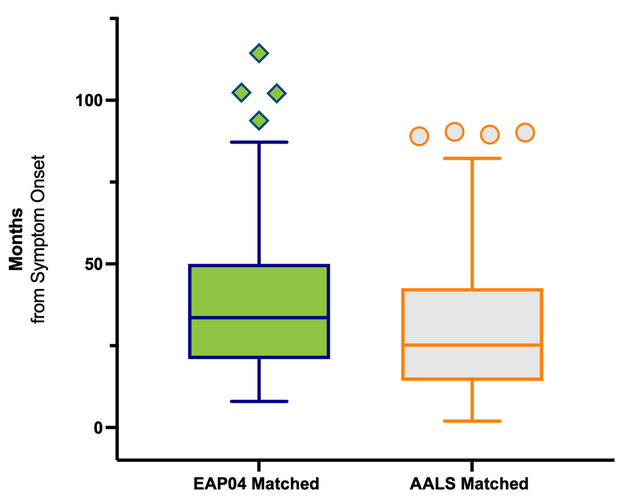
Propensity Matching Resulted in Balanced AALS Comparator Group

EAP04 Participants Had Slightly More Advanced Disease (> Onset Months, < ALSFRS-R)

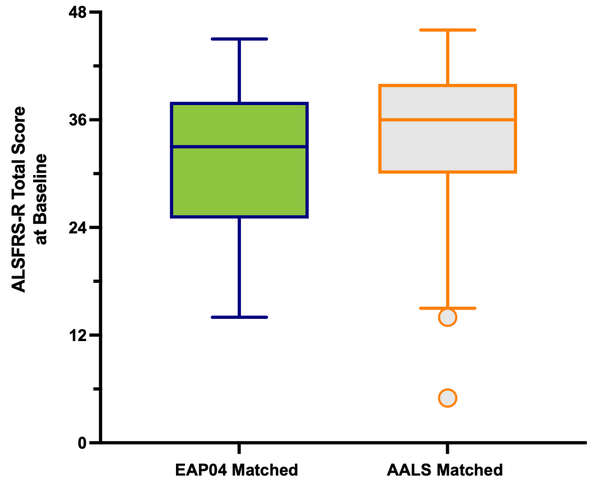
Age at Baseline
EAP04 and AALS Matched Participants (n=291)
(Tukey Box Plot, Median ± IQR, Limits: 1.5 x IQR)



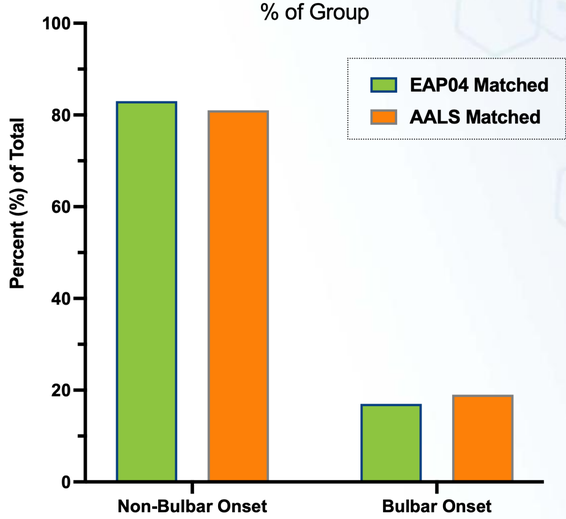
Months from Symptom Onset
EAP04 and AALS Matched Participants (n=291)
(Tukey Box Plot, Median ± IQR, Limits: 1.5 x IQR)



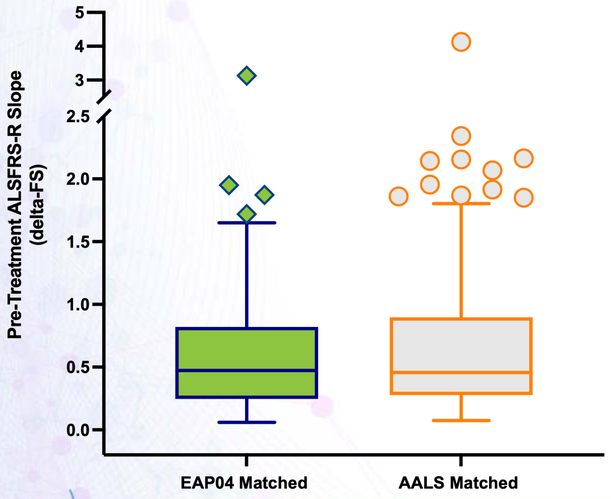
ALSFRS-R Total Score at Baseline
EAP04 and AALS Matched Participants (n=291)
(Tukey Box Plot, Median ± IQR, Limits: 1.5 x IQR)



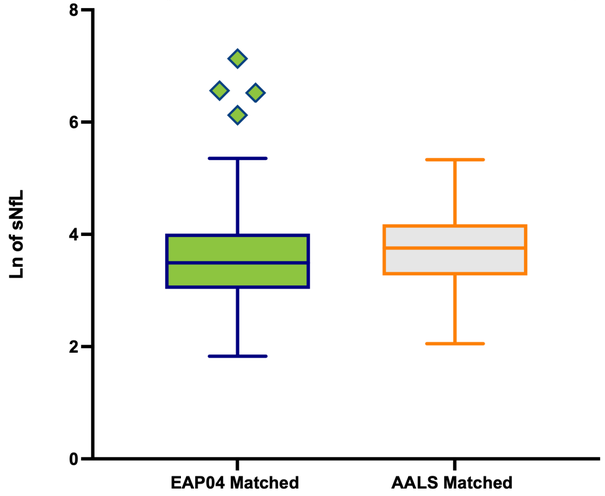
Symptom Onset Location Distribution
EAP04 and AALS Matched Participants (n=291)
% of Group



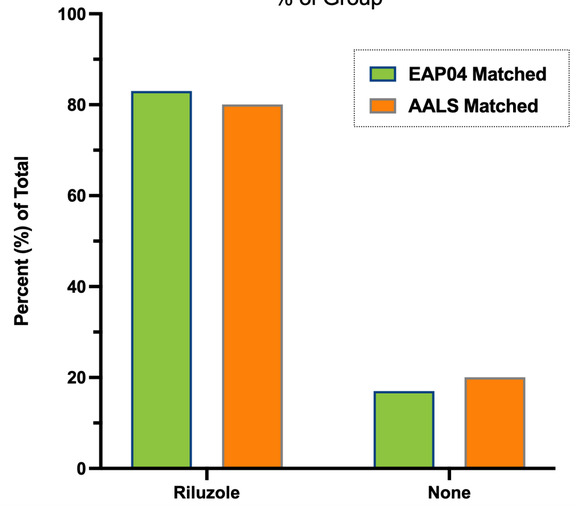
Pre-Treatment ALSFRS-R Slope (delta FS) at Baseline
EAP04 and AALS Matched Participants (n=291)
(Tukey Box Plot, Median ± IQR, Limits: 1.5 x IQR)



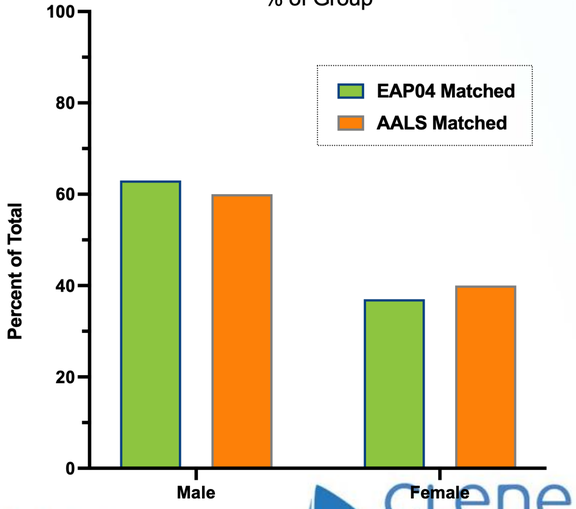
Ln(NfL) at Baseline
EAP04 and AALS Matched Participants (n=291)
(Tukey Box Plot, Median ± IQR, Limits: 1.5 x IQR)



Riluzole Treatment Distribution
EAP04 and AALS Matched Participants (n=291)
% of Group



Sex Distribution
EAP04 and AALS Matched Participants (n=291)
% of Group

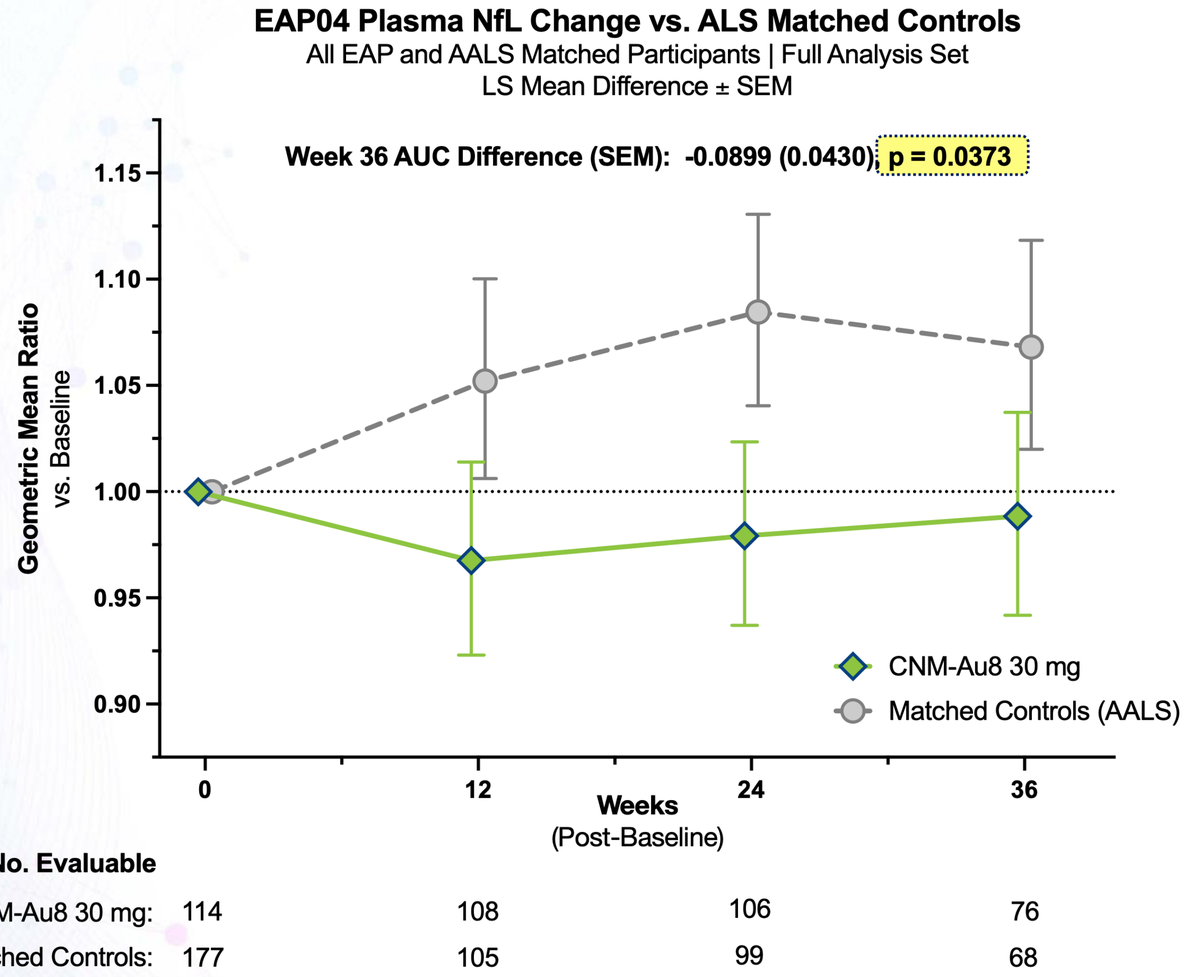


Data on File, Clene Nanomedicine, Inc.

EAP04 Interim NfL Analyses Results | Significant NfL AUC Difference

Comparison to AALS Matched Controls | Full Analysis Set (All Matched Participants)

Full Analysis Set AUC to W36 | All Matched Participants



EAP04 NfL Change vs. ALS Matched Controls
(Geometric Mean Ratio)

Period	AUC Difference GMR	95% CI	p-value
Week 24 AUC	0.911	0.836 – 0.993	p = 0.0339
Week 36 AUC	0.914	0.840 – 0.995	p = 0.0373
Week 48 AUC (Sensitivity)	0.918	0.846 – 0.997	p = 0.0412

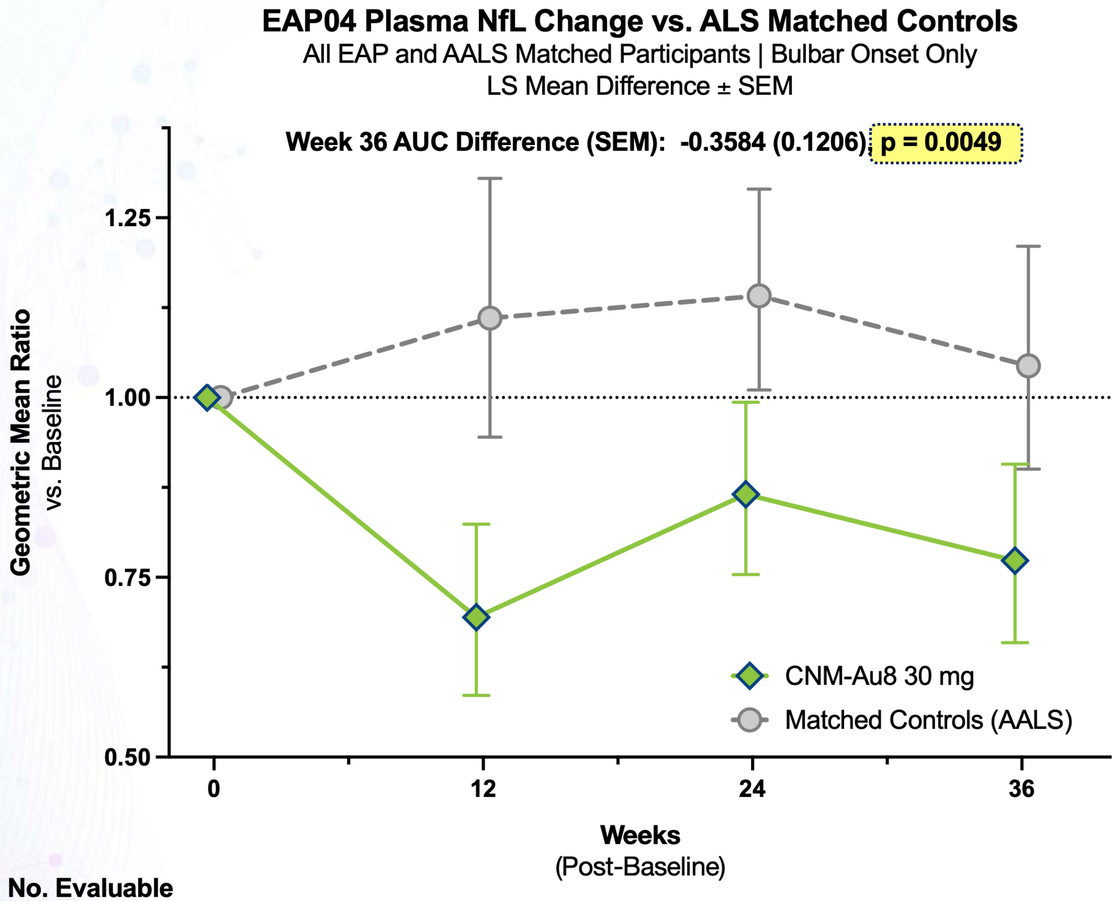
Model covariates are the same as those used for propensity matching: (i) Baseline Ln(sNfL), (ii) Sex, (iii) Riluzole Treatment, (iv) delta-FS, (v) Bulbar Onset, (vi) Age, and (vii) Months from Symptom Onset, and (viii) ALSFRS-R Total score

Data on File, Clene Nanomedicine, Inc.

EAP04 Interim NfL Analyses Results | Significant NfL AUC Difference

Comparison to AALS Matched Controls | All Bulbar Onset Matched Participants

Bulbar Onset AUC to W36 | All Matched Participants



No. Evaluable				
EAP04 CNM-Au8 30 mg:	19	18	19	13
AALS Matched Controls:	35	20	17	12

EAP04 NfL Change vs. ALS Matched Controls

(Geometric Mean Ratio)

Period	AUC Difference GMR	95% CI	p-value
Week 24 AUC	0.672	0.502 – 0.899	p = 0.0088
Week 36 AUC	0.699	0.548 – 0.891	p = 0.0049
Week 48 AUC (Sensitivity)	0.711	0.576 – 0.876	p = 0.0020

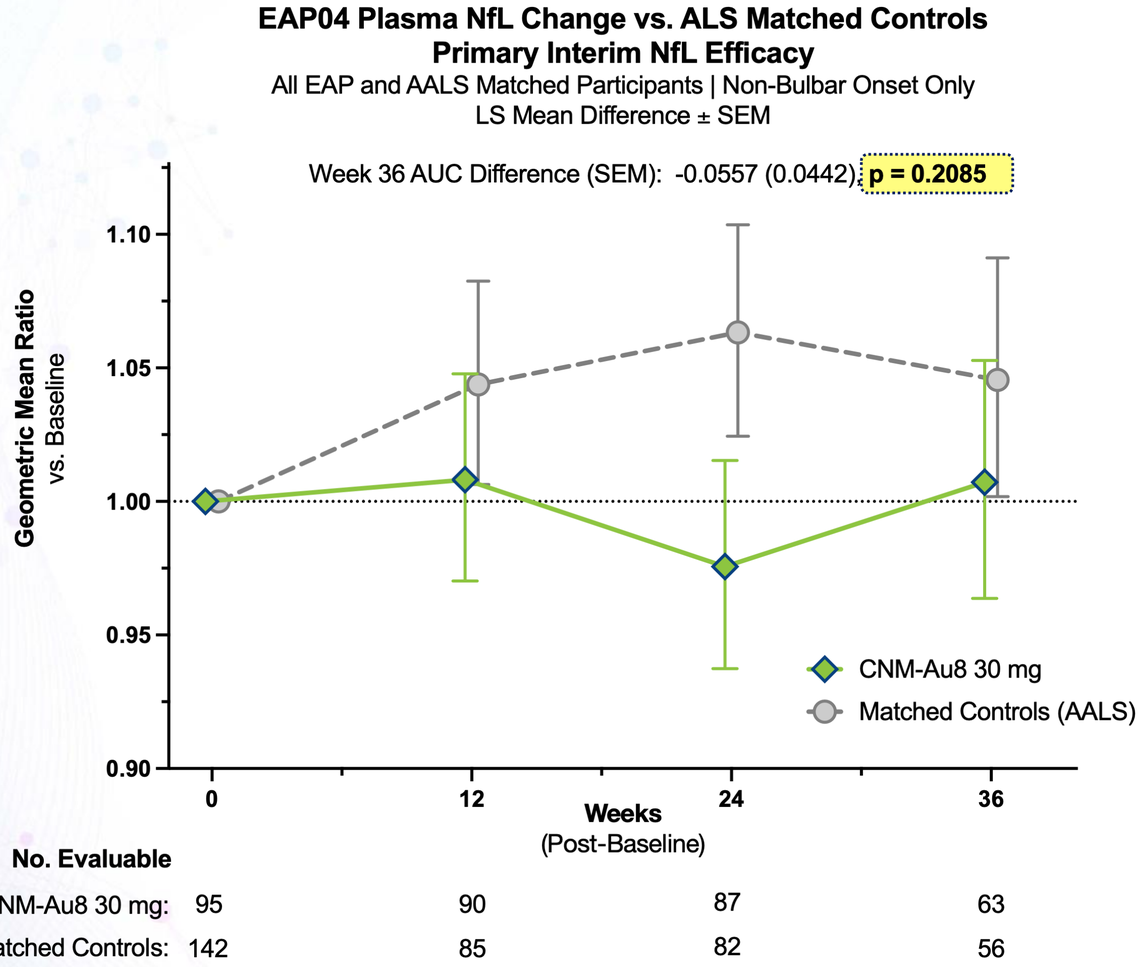
Model covariates are the same as those used for propensity matching: (i) Baseline Ln(sNfL), (ii) Sex, (iii) Riluzole Treatment, (iv) delta-FS, (v) Bulbar Onset, (vi) Age, and (vii) Months from Symptom Onset, and (viii) ALSFRS-R Total score

Data on File, Clene Nanomedicine, Inc.

EAP04 Interim NfL Analyses Results | AUC Difference at W36

Comparison to AALS Matched Controls | All Non-Bulbar Matched Participants

Non-Bulbar Onset AUC to W36 | All Matched Participants (Primary Efficacy Population for NfL Analysis)



EAP04 NfL Change vs. ALS Matched Controls

(Non-Bulbar Onset | Geometric Mean Ratio)

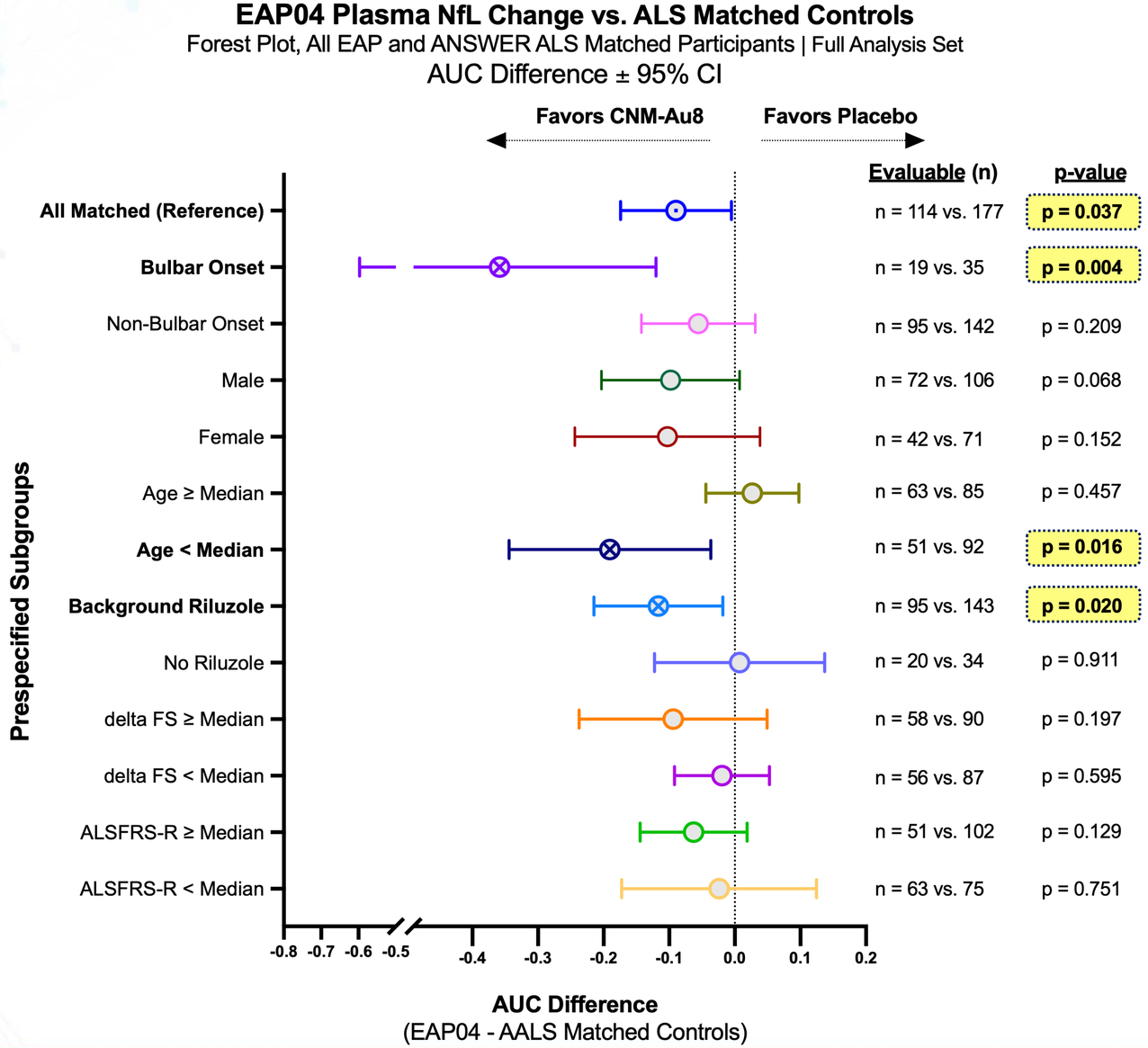
Period	AUC Difference GMR	95% CI	p-value
Week 24 AUC	0.942	0.863 – 1.027	p = 0.1752
Week 36 AUC	0.946	0.867 – 1.032	p = 0.2085
Week 48 AUC (Sensitivity)	0.944	0.867 – 1.028	p = 0.1854

Model covariates are the same as those used for propensity matching: (i) Baseline Ln(sNfL), (ii) Sex, (iii) Riluzole Treatment, (iv) delta-FS, (v) Bulbar Onset, (vi) Age, and (vii) Months from Symptom Onset, and (viii) ALSFRS-R Total score

Data on File, Clene Nanomedicine, Inc.

EAP04 Interim NfL Analyses Results | Significant NfL AUC Difference

Comparison to AALS Matched Controls | Prespecified Subgroups



Model covariates are the same as those used for propensity matching: (i) Baseline Ln(sNfL), (ii) Sex, (iii) Riluzole Treatment, (iv) delta-FS, (v) Bulbar Onset, (vi) Age, and (vii) Months from Symptom Onset

Data on File, Clene Nanomedicine, Inc.

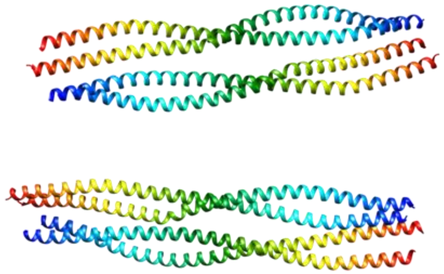
Why Area Under the Curve (AUC)?

- **AUC** is generally more informative when correlating with survival in ALS because ALS is dynamic, continuously evolving disease and neurofilament levels fluctuate over time
- AUC captures the total burden of neuroaxonal injury-single time point gives a snapshot , AUC integrates the concentration over time representing the cumulative exposure to neurodegeneration so conceptually,
  - a single time point →"What is the level today" vs. AUC→"How much axonal injury has accumulated over this period"

- Conceptual analogy: Think of NfL as smoke from a fire
- A single measurement = how smoky the room is RIGHT NOW
- AUC= how much smoke filled the room over the WHOLE NIGHT
- The second tells you much more about how big the fire actually was

NYU Langone Health

Investigating GFAP in ALS



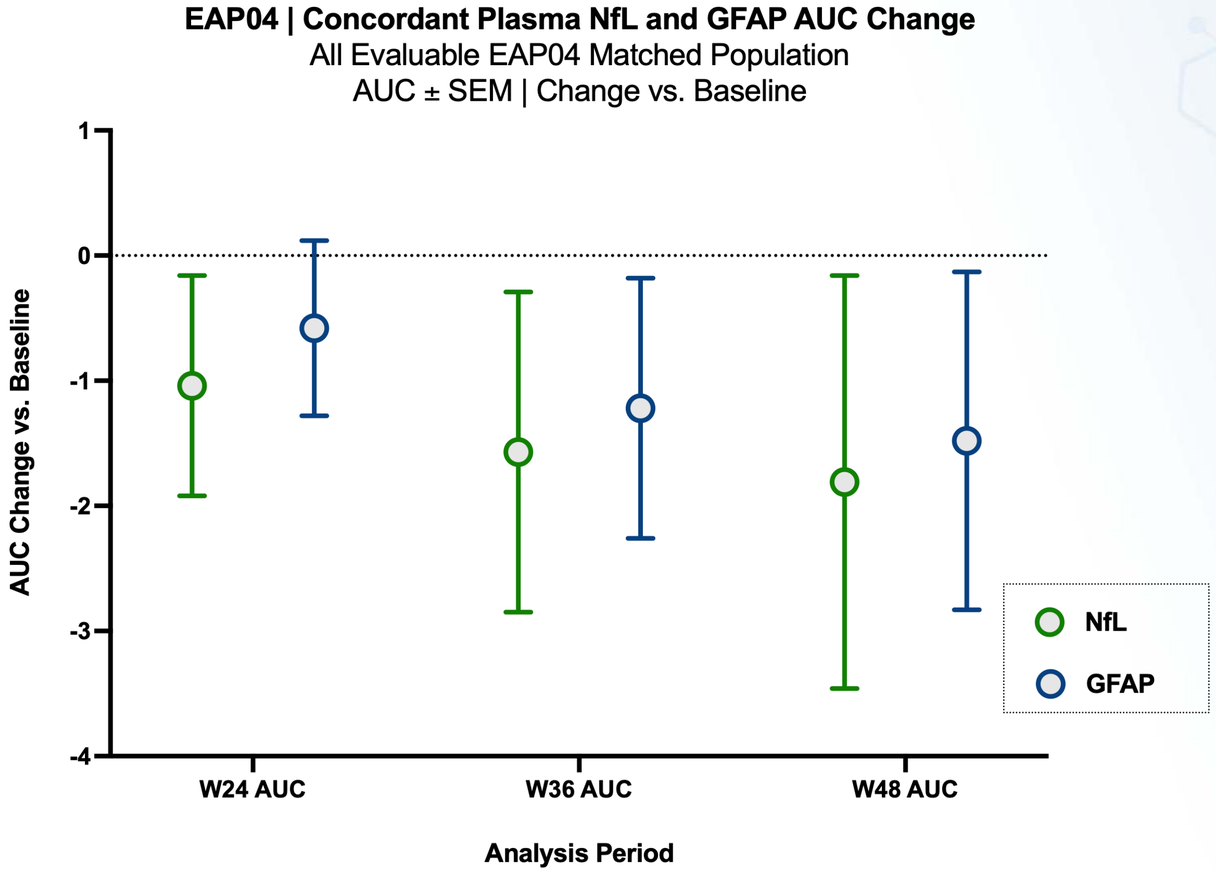
- A prospective multicenter study showed that Glial fibrillary acidic protein(GFAP) predicted survival in ALS (Jung et al. J Neurol 2025)
- Hypothesis: CNM-Au8 may reduce astrocytic reactivity **not by acting directly on GFAP expression,** but by improving the *bioenergetic environment* of neurons and glia, reducing oxidative stress, and normalizing inflammatory signaling
- Astrocytic reactivity in ALS is heavily driven by metabolic failure, mitochondrial stress, and neuron-derived danger signals—all of which CNM-Au8 targets upstream

NYU Langone Health

EAP04 | Strong Concordance between NfL and GFAP Decline

Consistency of Effect on NfL and GFAP Change

EAP04 AUC Period	Pearson r	p-value	Concordance
Week 0 – 24 AUC	0.911	p < 0.001	80.9%
Week 0 – 36 AUC	0.919	p < 0.001	78.3%
Week 0 – 48 AUC	0.941	p < 0.001	78.3%



Data on File, Clene Nanomedicine, Inc.

EAP04 | Interim NfL Analyses Conclusions

- CNM-Au8 30 mg treatment resulted in significant NfL declines compared to matched controls from AALS within the Full Analysis Set

  - Consistent treatment effects were observed across comparison periods:
    - AUC to Week 24 (Concordant with HEALEY analysis period)
    - AUC to Week 36 (Primary Analysis Period)
    - AUC to Week 48 (Sensitivity Analysis)

- Effect in the Primary Efficacy Population (Non-Bulbar Onset) was not significant

- Consistent Effect Across Plasma NfL and GFAP Decline

Data on File, Clene Nanomedicine, Inc.

Acknowledgements

- We sincerely thank the participants and their families for their invaluable contributions to Study EAP04 and ANSWER ALS
- We also acknowledge the site investigators and clinical support staff for their essential role in facilitating neurofilament light chain (NfL) sample collection for these analyses and BioSEND for their biorepository services.
- We gratefully recognize the support of ACT for ALS and the NIH grant funding Study EAP04
- NfL and clinical data used in these analyses were obtained from the Answer ALS Foundation Program through the ANSWER ALS Data Portal (AALS-01184). For up-to-date information on the study, please visit https://dataportal.answerals.org.

ACT FOR ALS

- ***GRANTS FOR RESEARCH ON THERAPIES FOR ALS:*** *Grant program that funds access to investigational therapies currently in development from small biotechnology companies for those patients who cannot participate in clinical trials while supporting research on how these investigational therapies impact the disease.*
- **HHS PUBLIC-PRIVATE PARTNERSHIP FOR RARE NEURODEGENERATIVE DISEASES:** Establishes an HHS Public-Private Partnership for rare neurodegenerative diseases to advance the understanding of these diseases and foster the effective development and evaluation of treatments
- **ALS AND OTHER RARE NEURODENERATIVE DISEASE ACTION PLAN** – commissioned the publication of FDA Action Plan (6/2023) to support drugs that improve and extend the lives of people and facilitate access to investigational drugs for those living with ALS and other are neurodegenerative disease
- **FDA RARE NEURODEGENERATIVE DISEASE GRANT PROGRAM:** FDA grant program to fund research and therapy development for ALS and other life threatening or severely debilitating rare neurodegenerative diseases

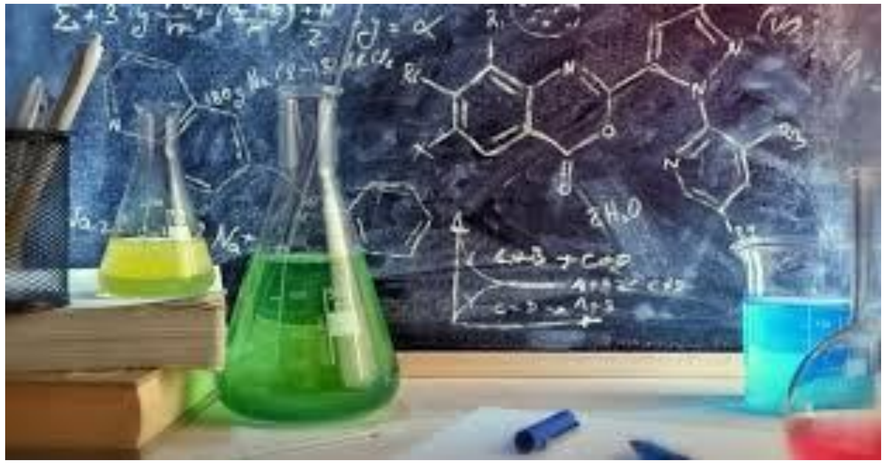
Innovation and Scientific Rigor in NIH-Funded EAP Programs

- **INNOVATION**
- Flexible study designs with options for remote visits, testing feasibility of fully remote enrollment, remote collection of data
- Evaluation of **novel** digital outcome measures, longitudinal clinical data and biomarker samples
- Study data and biofluid samples from ALL NIH funded EAPS go into **central repository** after study completion maintained by NIH for open science
- Evaluating the use of virtual or ‘synthetic’ controls and application of historical controls

- **RESEARCH / SCIENTIFIC RIGOR**
- These EAPs have full data monitoring for data validity and reliability
- They are collecting patient reported outcomes (PROs), function, survival and clinical and digital biomarkers for efficacy analyses
- They employ regulatory standard clinical monitoring, DSMB, steering committees and safety reporting similar to traditional clinical trials

Scientific Research

- **FUNDING SUPPORTS SCIENTIFIC RESEARCH EMBEDDED BEYOND ACCESS TO INVESTIGATIONAL DRUGS IN THESE EAP PROGRAMS:**
- All EAPS have research aims other than just providing access to investigational products that can augment our biological understanding of ALS
  - Studying novel clinical outcomes that can be used for future clinical trials
  - Evaluating candidate biomarkers that can help understand ALS biology and help to identify/classify subgroups, target therapy (precision therapy) based on biomarkers, and improve means of measuring disease progression



- **BIOSEND:** All EAPS contribute samples to the same scalable, sustainable central repository for ALS maintained by NIH
- **NeuroGUID:** All information and samples collected from all NIH funded EAP/Natural History studies are collected in a standardized fashion and use Global Unique Identifiers
- **KNOWLEDGE PORTAL:** All information and samples will be freely accessible to all researchers enhancing OPEN SCIENCE

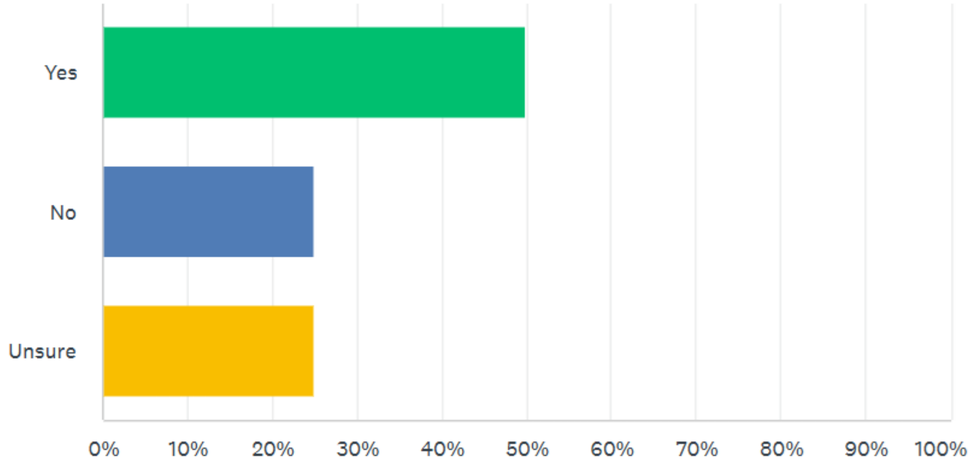
BUILDING A MORE ROBUST ALS RESEARCH LANDSCAPE FOR THE FUTURE

THESE PROGRAMS ARE CONTRIBUTING TO A MORE ROBUST INFRASTRUCTURE FOR ALS RESEARCH IN THE FUTURE

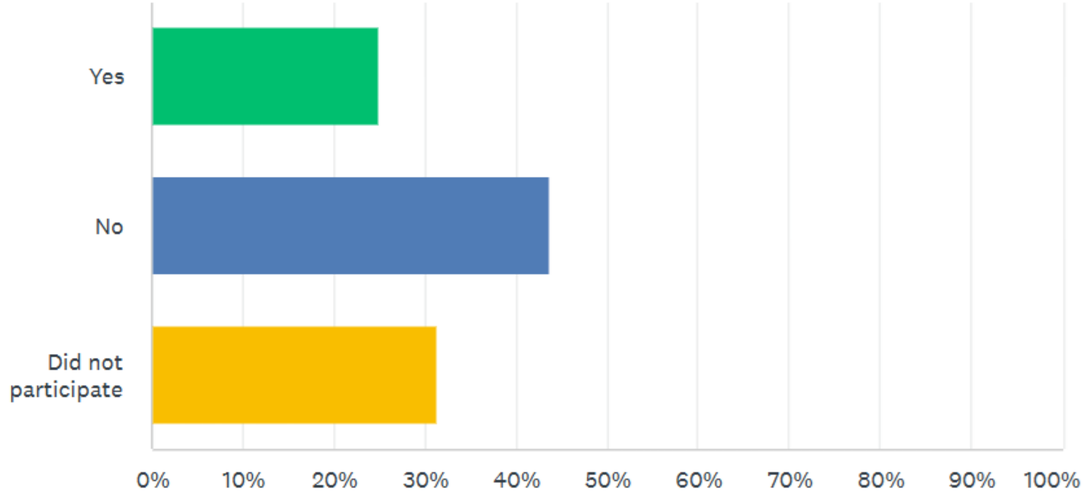
- Clene EAP → first attempt at fully remote enrollment across the United States
- Pridopidine EAP → includes new sites including smaller community hospital and neurology private practice group to build research capacity for more centers to be involved in ALS research in the future
- RAPA501 EAP → broadening the number of centers that can develop interdisciplinary expertise in ALS and cell therapy
- Learnings from the setup of these EAPs has led to efficiency for future research programs

ACT for ALS increased ability and capacity at ALS CENTERS

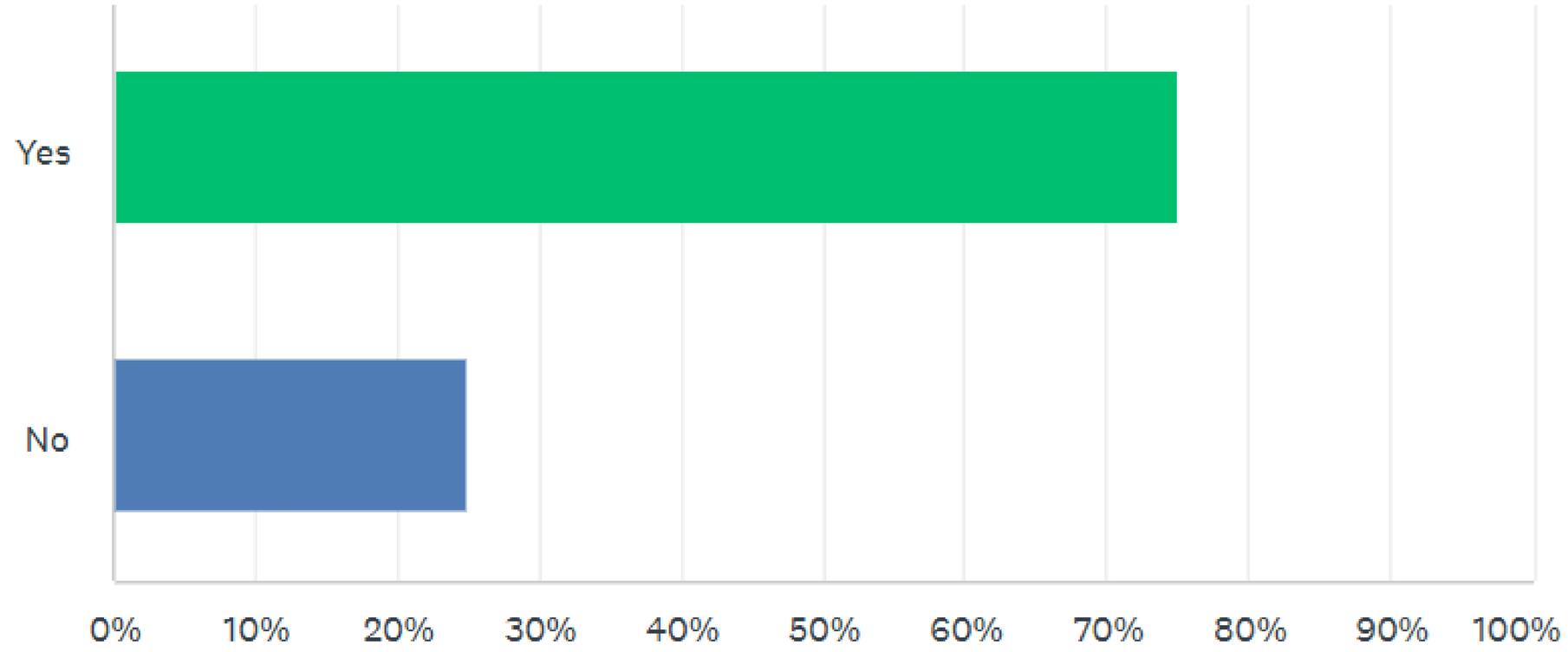
Has participating in an NIH-funded EAP or ALL ALS helped build your site's capacity for ALS research?

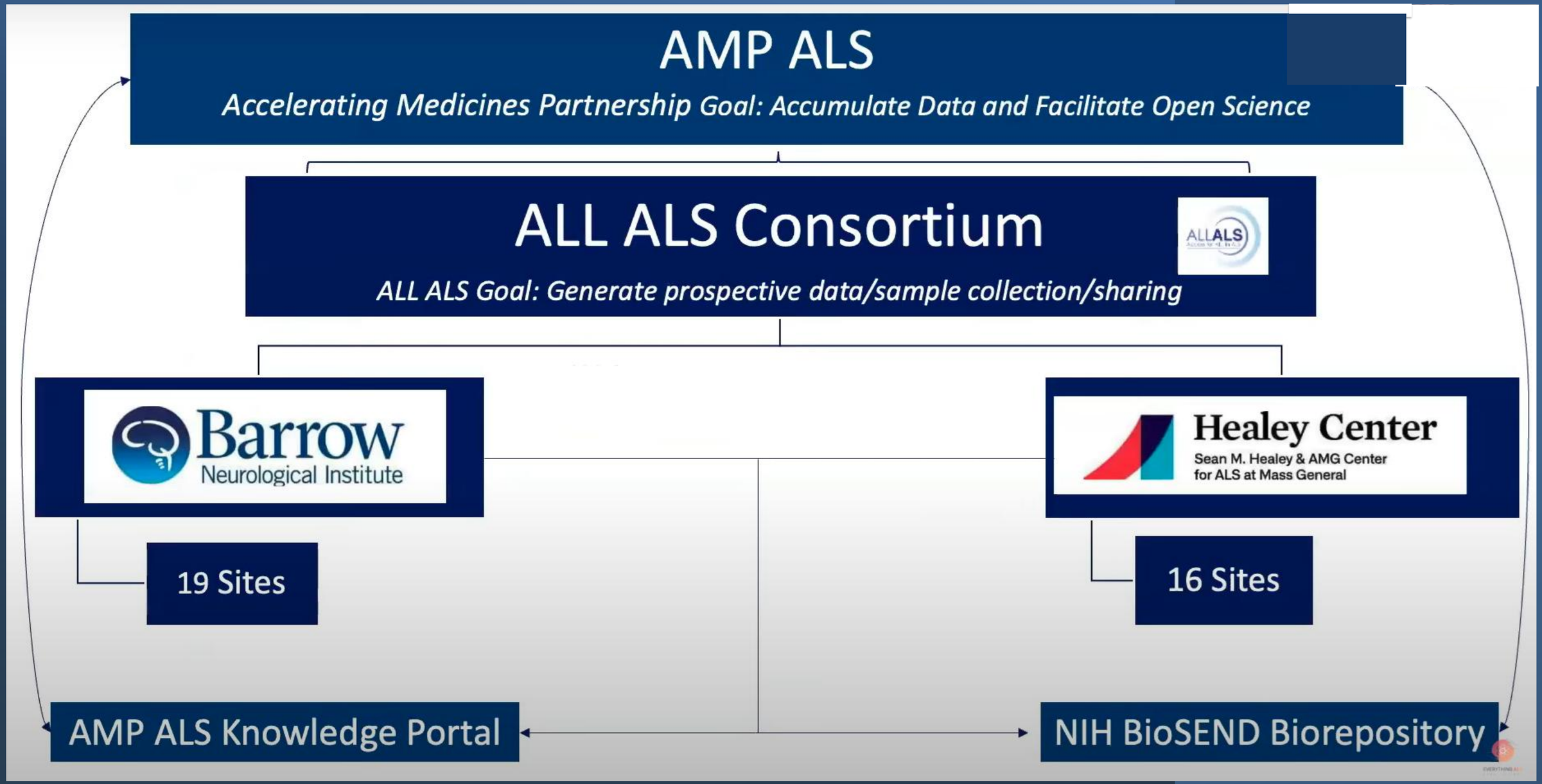


Was this the first EAP you led at your site?

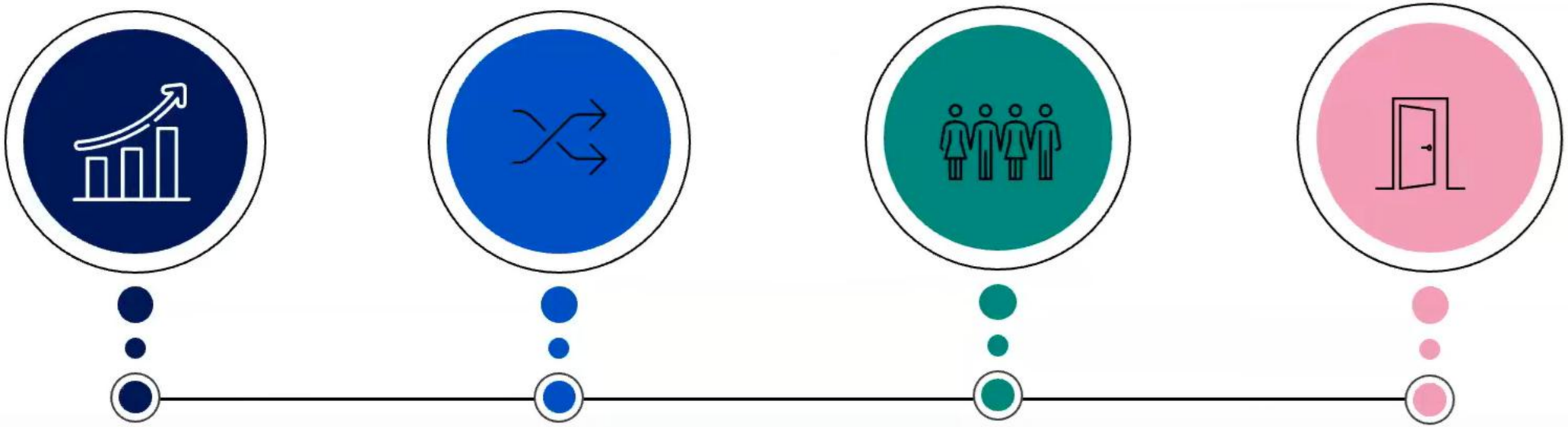


Is your site now participating in ALL ALS?




AMP ALS
Accelerating Medicines Partnership Goal: Accumulate Data and Facilitate Open Science
ALL ALS Consortium
ALL ALS Goal: Generate prospective data/sample collection/sharing
ALLALS
Barrow
Neurological Institute
Healey Center
Sean M. Healey & AMG Center
for ALS at Mass General
19 Sites
16 Sites
AMP ALS Knowledge Portal
NIH BioSEND Biorepository

What are the Goals of ALL ALS?



Accelerate Research Outcomes

Collecting large amounts of data to share with researchers around the world!

Integration

Combining data from past and current studies to fill in gaps in natural history knowledge

Community

Feel connected through community webinars, newsletters, and social media

Accessibility

Participate at one of the 35 clinical sites, or completely remotely!

CDC

TARGET ALS

FNIH Foundation for the National Institutes of Health

Clinic-Based Multi-Site ALS Natural History & Biofluid Study

Summary

ACT for ALS created partnerships to coordinate and create prioritized research and funding for the ALS community

FDA priorities

NIH Strategic Planning Working Group

National Academies Report

Partnership and studies with AMP ALS, Critical Path Institute, FDA, and NIH

Without NIH-funded EAP → although there is a desire to make more slots available in the current programs, there would significantly less availability to the community without this program

ALL-ALS is the largest, sustainable, natural history study of symptomatic, at risk, and control individuals which is synergized with data collected via ALL NIH funded EAP programs AND existing data repositories → available via OPEN SCIENCE

ACT for ALS has catalyzed the field to build infrastructure for research, contribute to scientific research in ALS, broaden access to investigational drugs, and developing a standardized, centralized, and sustainable natural history repository that has been limited due to funding previously

Thank you!