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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Chief Scientific Officer

Professor and Chair, Department of Translational Neuroscience

Barrow Neurological Institute, Phoenix, AZ

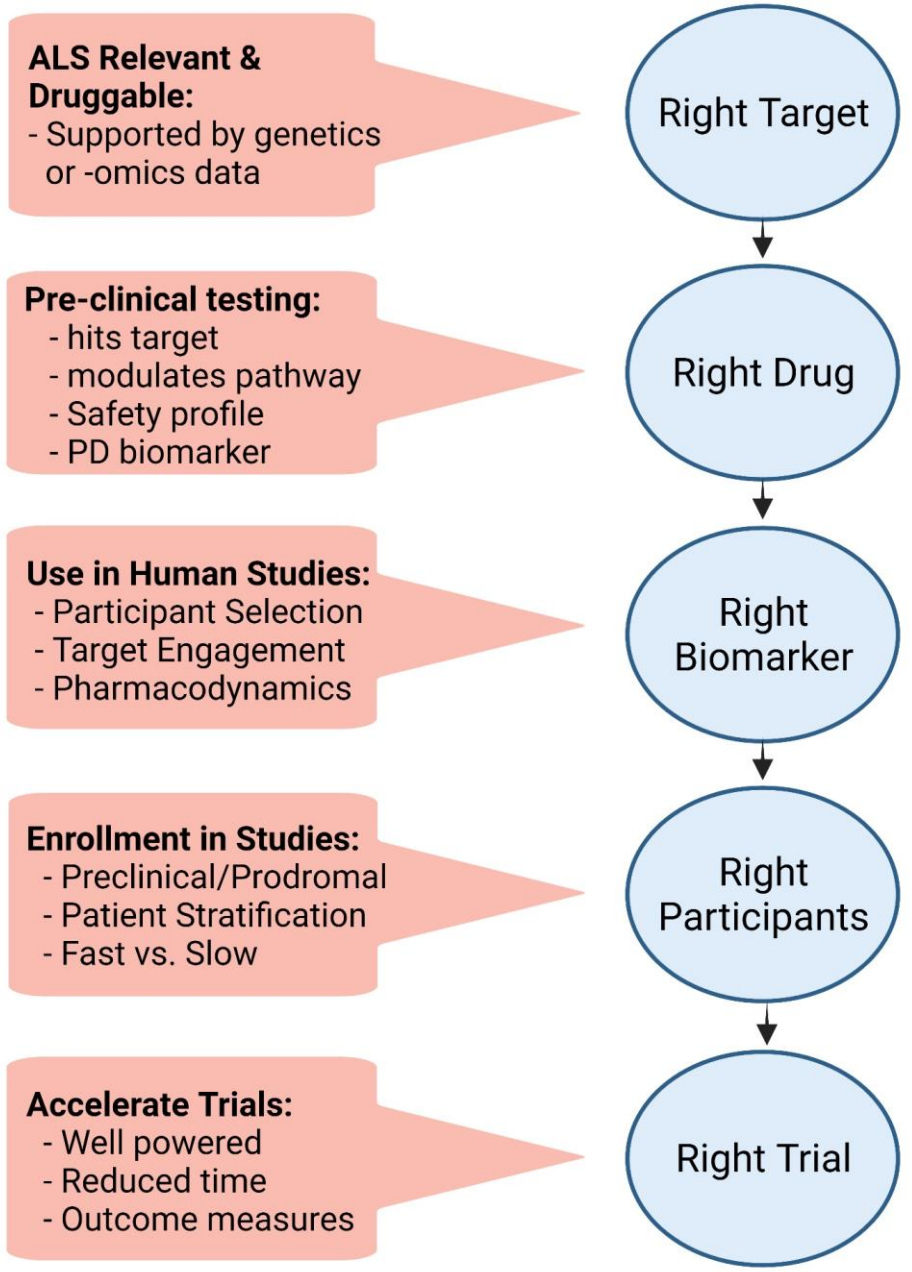
May 30, 2024

Sources of Biomarkers

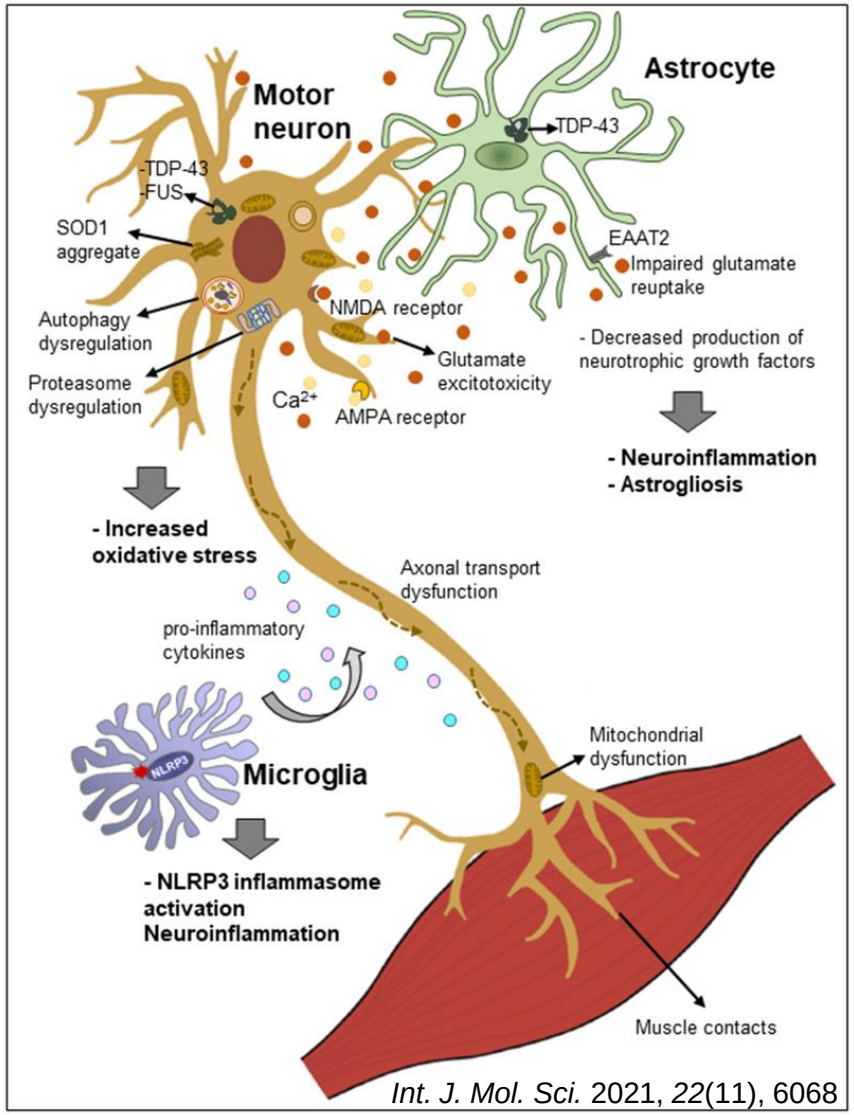
- Genetic: Gene mutations or repeat expansions; Risk factors; Gene expression or splicing alterations
- Biofluid: CSF, Blood, Urine, Saliva
- Tissue: Muscle, Skin, Post-mortem tissues
- Digital: Speech, Movement
- Imaging: PET, MRI, DTI

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



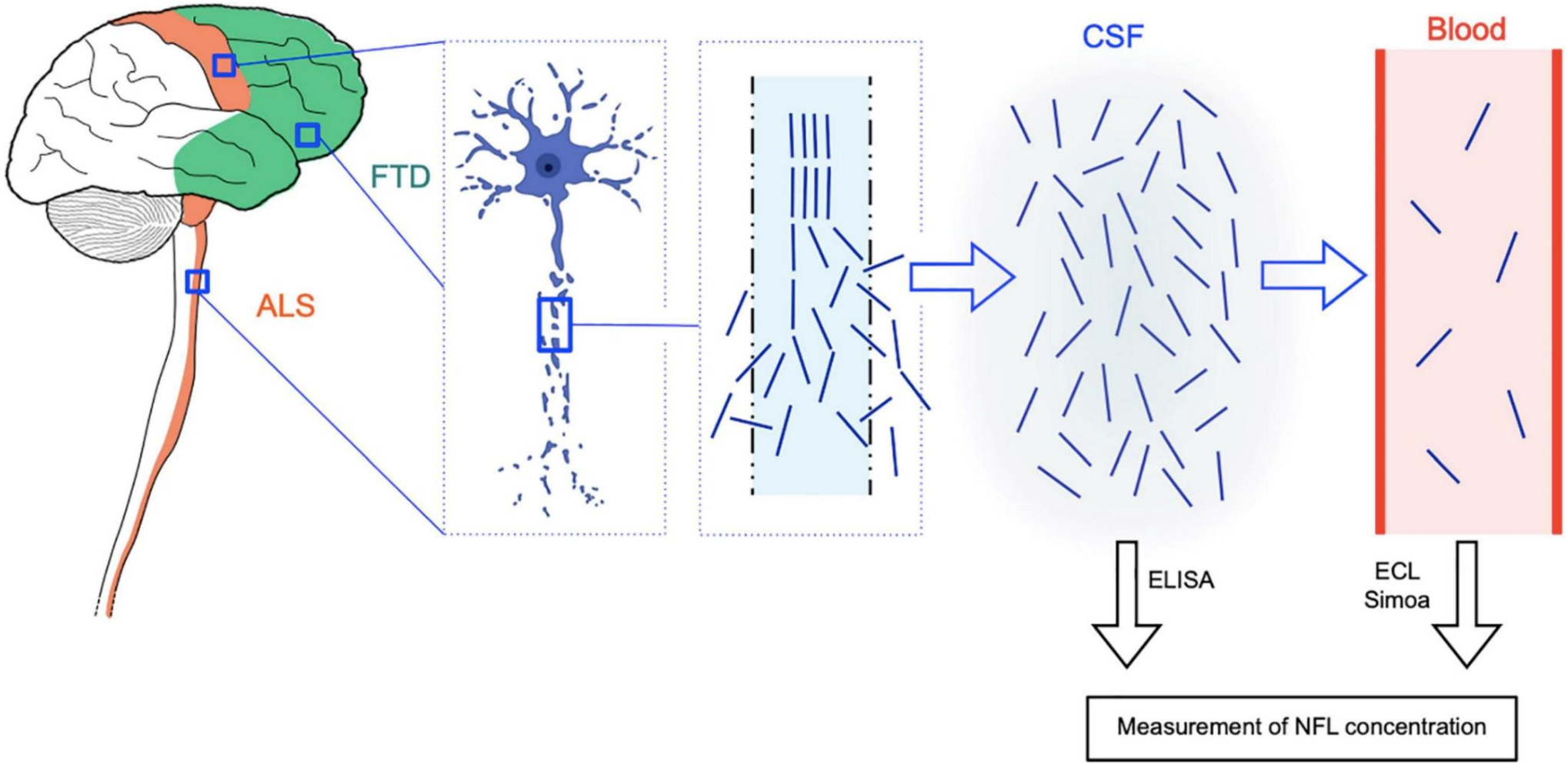
Fluid-based biomarkers to monitor ALS disease progression and/or treatment response



Int. J. Mol. Sci. 2021, *22*(11), 6068

- 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

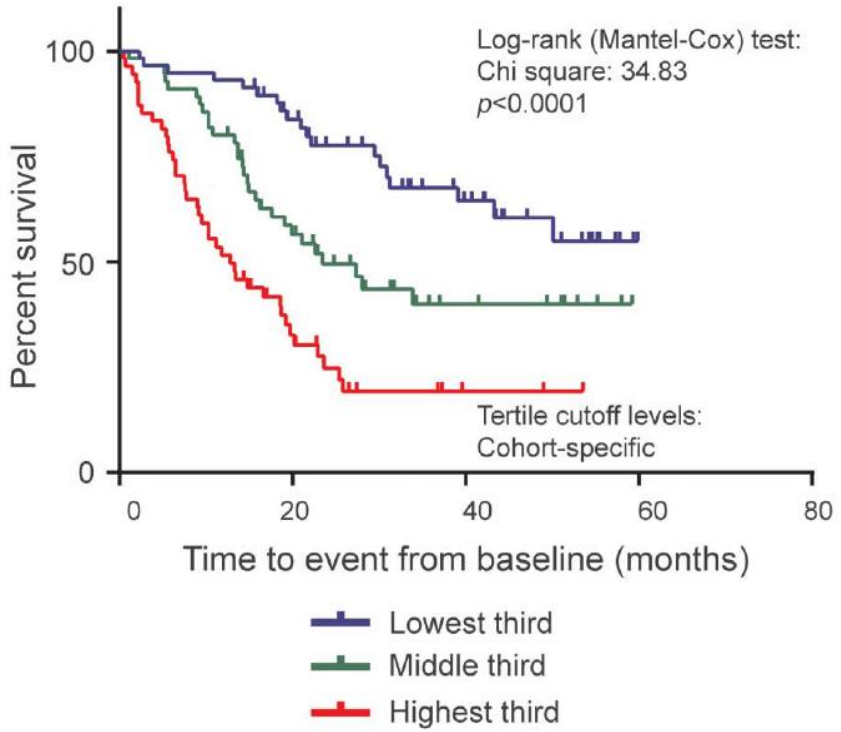
Neurofilament is the Top Protein Biomarker for ALS and FTD



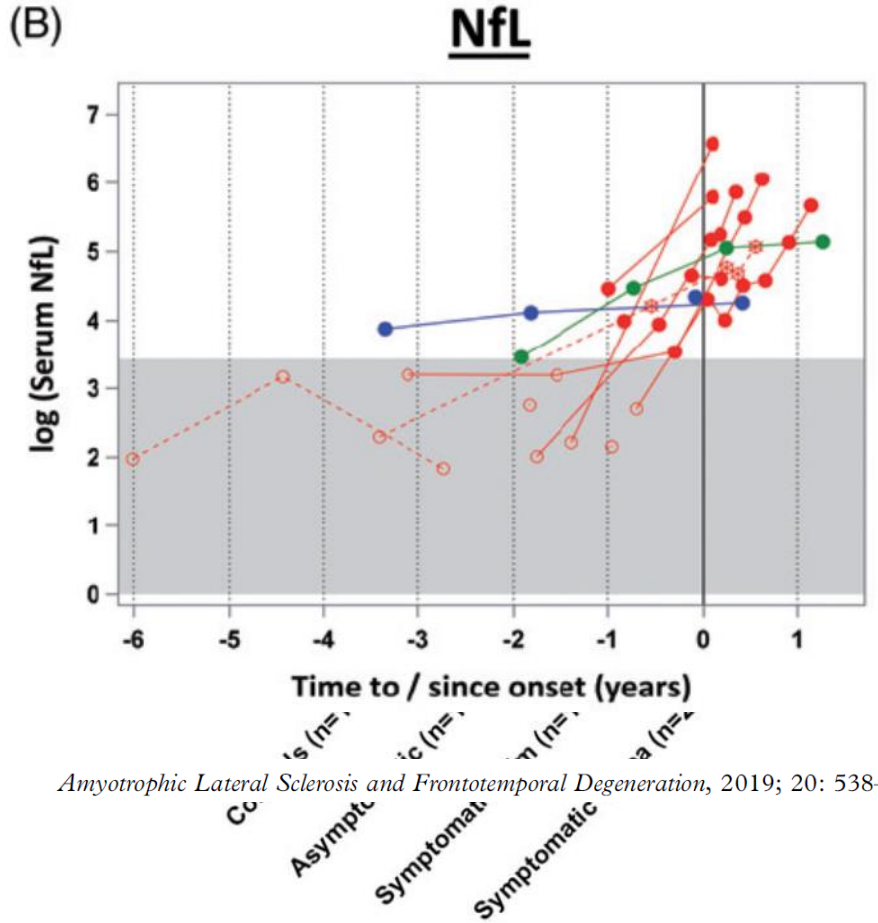
Front. Neurosci. 15:679199. (2021)

NFL as a Prognostic Biomarker

Biofluid levels correlate to rate of disease progression



Increases before symptom onset in asymptomatic gene carriers

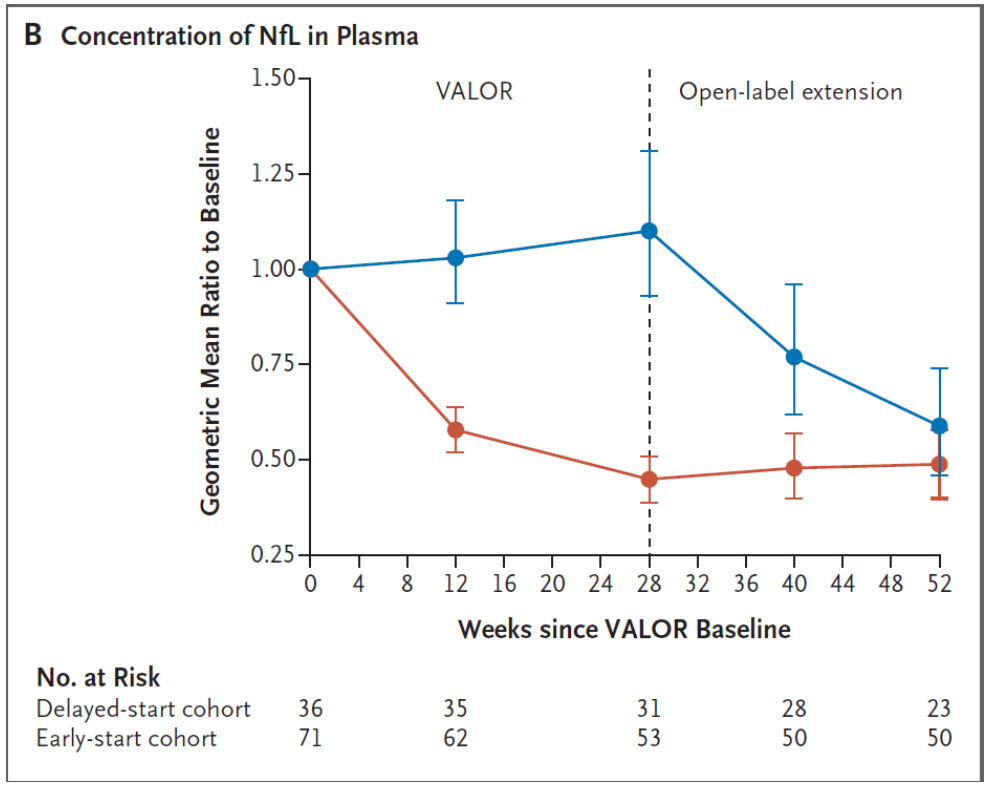


Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2019; 20: 538–548

ANN NEUROL 2016;79:152–158

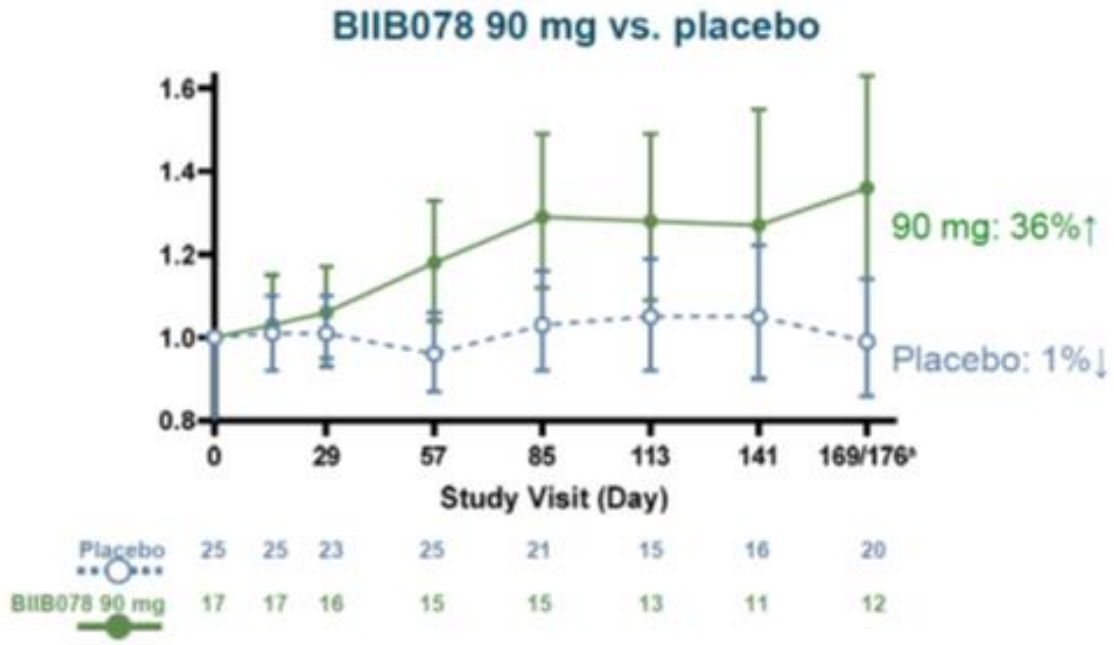
NFL as a Response to Drug Treatment

Decreased NFL in response to SOD1 ASO treatment



N Engl J Med 2022; 387:1099-1110

Increased NFL in response to C9 ASO treatment



Courtesy of Biogen and Ionis

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

Biomarkers for Rate of Disease Progression

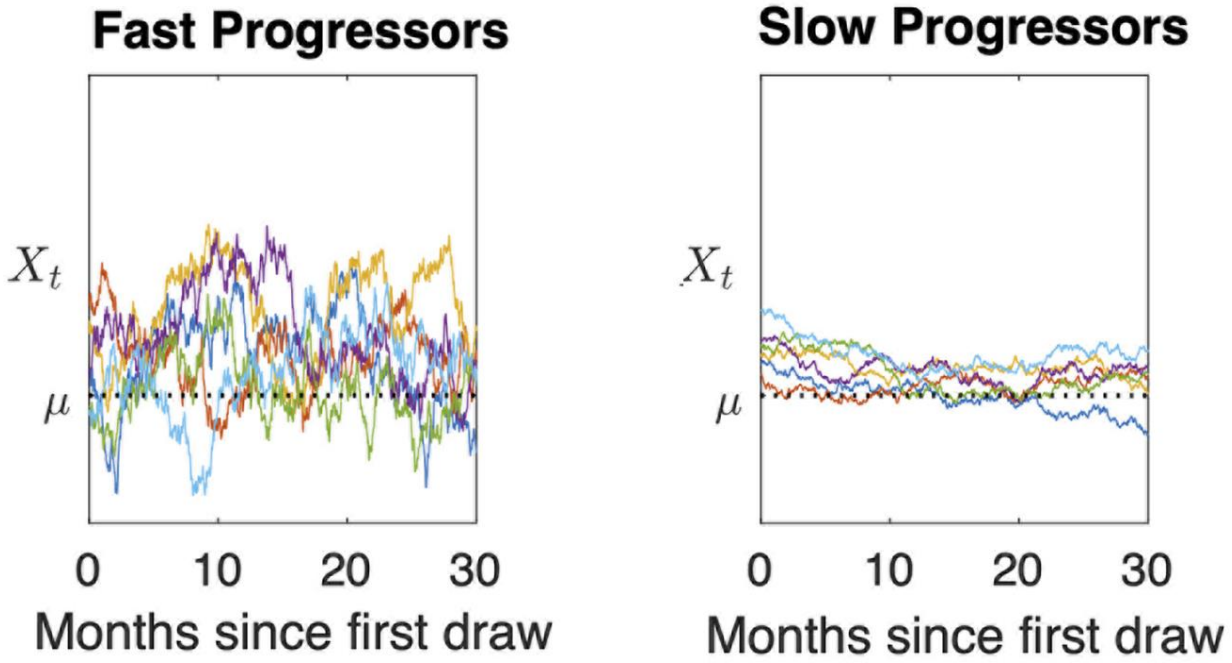
ANNALS of Clinical and Translational Neurology
Open Access
AMERICAN NEUROLOGICAL ASSOCIATION
INNOVATORS IN DISCOVERY, EDUCATION, AND CARE

RESEARCH ARTICLE *Ann Clin Transl Neurol.* 10:2025-2042 (2023)

Proteomics and mathematical modeling of longitudinal CSF differentiates fast versus slow ALS progression

Lucas Vu[1], Krystine Garcia-Mansfield[2,3], Antonio Pompeiano[4], Jiyan An[1], Victoria David-Dirgo[3], Ritin Sharma[2,3], Vinisha Venugopal[1], Harkeerat Halait[1], Guido Marcucci[5], Ya-Huei Kuo[5], Lisa Uechi[6], Russell C. Rockne[6], Patrick Pirrotte[2,3,#] & Robert Bowser[1,#]

Mass spectrometry proteomics of CSF identified significant global variations in the proteome that distinguished fast and slow progressors.



Biomarkers for Rate of Disease Progression

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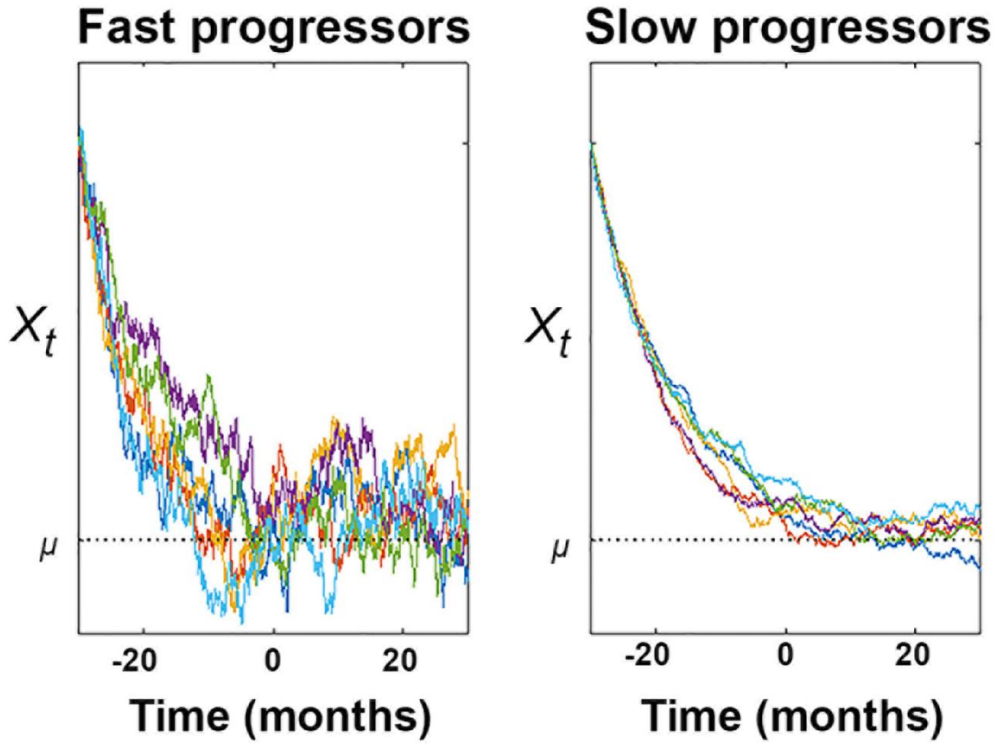
A mathematical model was generated that can predict who is a fast or slow progressor using mass spectrometry proteomics of a single CSF sample.



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)

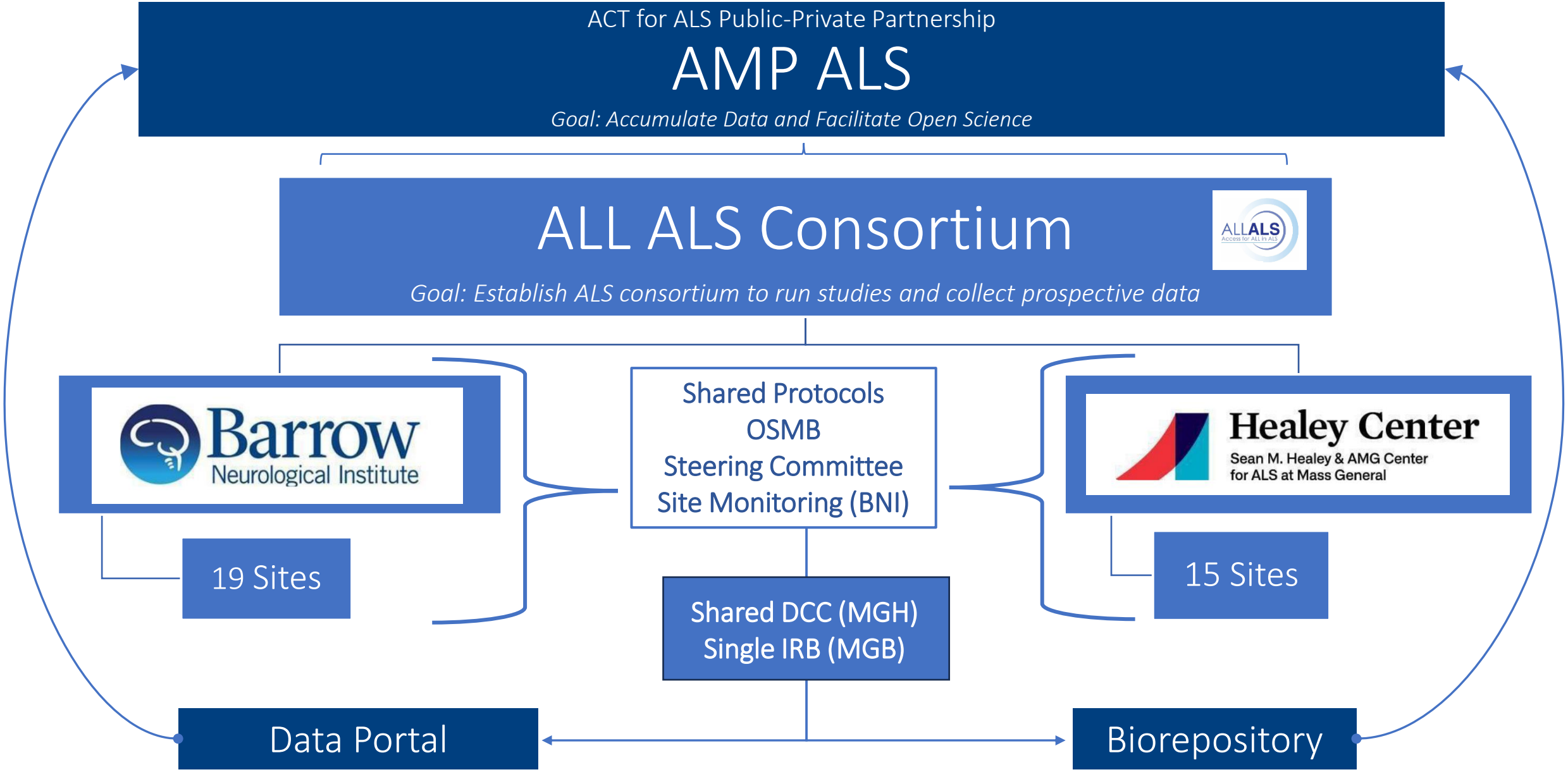

ALLALS
Access for ALL in ALS

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
ALLALS
Access for ALL in ALS
Barrow
Neurological Institute
19 Sites
Shared Protocols
OSMB
Steering Committee
Site Monitoring (BNI)
Shared DCC (MGH)
Single IRB (MGB)
Healey Center
Sean M. Healey & AMG Center
for ALS at Mass General
15 Sites
Data Portal
Biorepository

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
- ❑ John Hopkins University
- ❑ Houston Methodist

ALL ALS Enrollment Objectives

Enroll >2000 participants quickly!

Think Large and Inclusive

- Geography
- Race/ethnicity
- Socio-economic status
- Education level

Coordinate with ongoing studies

- Target ALS
- Natural History study
- PREVENT ALS

Reduce Barriers to Participation

- Engage Study Sites
- Learn from People Living with ALS

Outreach activities & communication

- ALS Association, MDA
- IAMALS, Everything ALS, etc.
- Community engagement science

Decentralized Study Methodology

ALLALS
Access for ALL in ALS

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

ALLALS
Access for ALL in 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 - STUDY DESIGN

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

Cognitive Testing:
ECAS + FTLD-CDR

ePROs

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