Thank you for joining the weekly webinar!

We are admitting audience members from the waiting room.

Please allow a few moments for the webinar to begin.

HEALEY ALS Platform Trial

Weekly Q&A – February 22, 2024

Massachusetts General Hospital
Founding Member, Mass General Brigham

HARVARD MEDICAL SCHOOL

Healey & AMG Center

Sean M. Healey & AMG Center for ALS
at Massachusetts General Hospital

TACKLE ALS "DON'T BE SORRY LETS BEAT THIS"

ALS ASSOCIATION

MDA Muscular Dystrophy Association

SALSA For a Cure

alsFINDINGaCURE

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

IAM ALS

TAMBOURINE

NCRI NEUROLOGICAL CLINICAL RESEARCH INSTITUTE

BARROW Neurological Institute

ALS ONE

RUN2REVIVE MIND · BODY · POTENTIAL

Berry Consultants Statistical Innovation

1850 MELIORA

ucb

biohaven pharmaceuticals

CLene NANOMEDICINE

prilenia

THE ARTHUR M. BLANK FAMILY FOUNDATION

BASEBALL WINTER MEETINGS SAN DIEGO 2015

SEELOS THERAPEUTICS

Calico

DENALI THERAPEUTICS

AMG The AMG Foundation

Patient Navigation

Central resource for people living with ALS

Catherine Small

Allison Bulat

Phone: 833-425-8257 (HALT ALS)

E-mail:healeyalsplatform@mgh.harvard.edu

Weekly webinar registration:

https://bit.ly/3r6Nd2L

ALS Link sign-up:

https://bit.ly/3o2Ds3m

Upcoming Webinars:

February 29th- Weekly Q&A

March 7th- Weekly Q&A

March 14th- EAP Discussion with Dr. Jinsy Andrews (Columbia University)

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Sean M. Healey & AMG Center for ALS
at Massachusetts General Hospital

Genetics of ALS

Mark Garret, MD

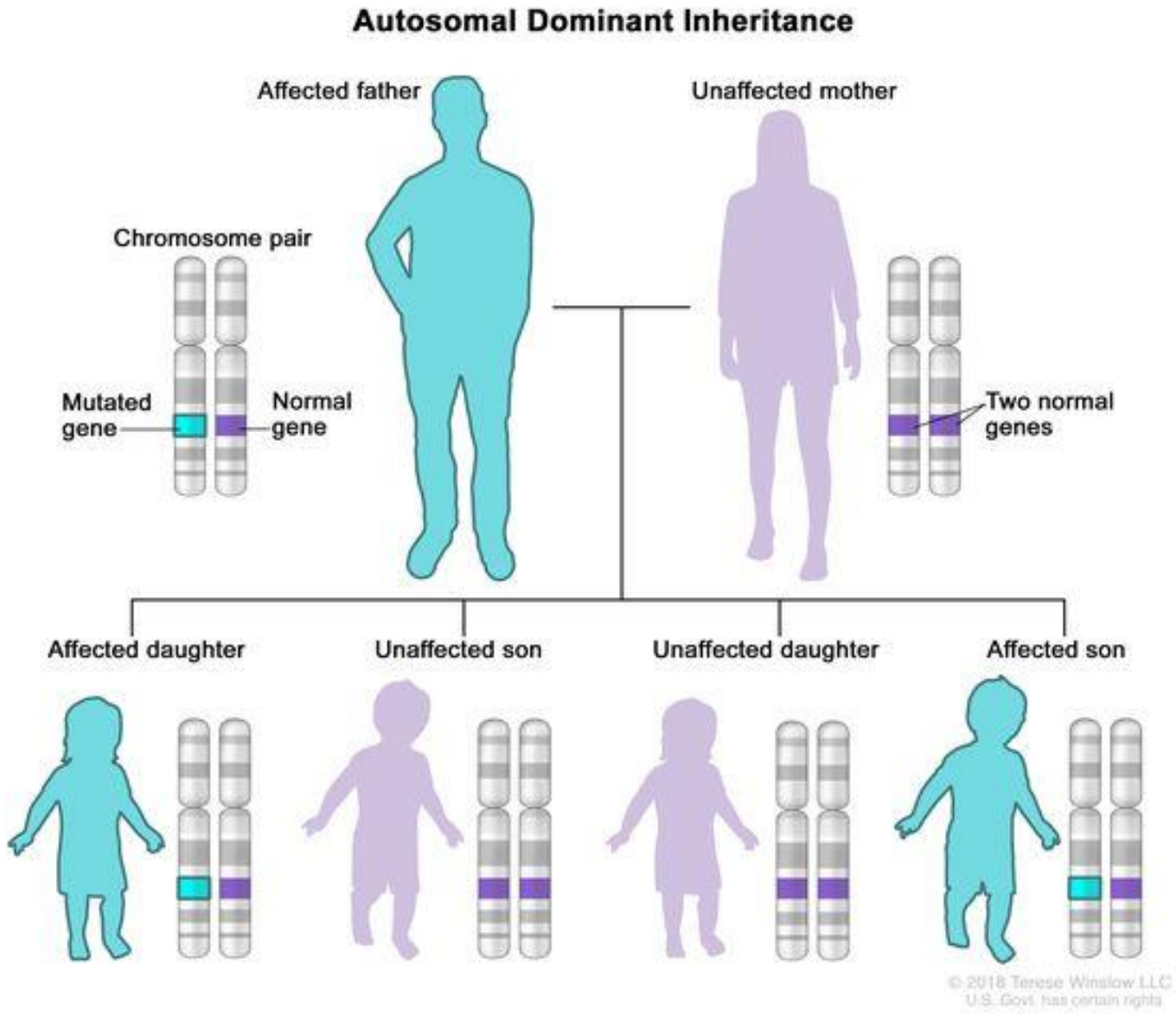
Healey & AMG Center
Sean M. Healey & AMG Center for ALS
at Massachusetts General Hospital

Is ALS inherited?

“Familial” or “Genetic” ALS

- 15% of ALS is caused by a changes in a single gene
- Familial ALS = Multiple family members with ALS or related diseases (Frontotemporal Dementia; FTD)
  - 10% of ALS

BUT 5% of “sporadic” ALS patients have causative genetic variants identified when genetic testing is performed



cancer.gov

Dominant Inheritance:

- One abnormal copy of a gene can cause ALS
- 50% risk of a parent passing that gene to a child regardless of sex

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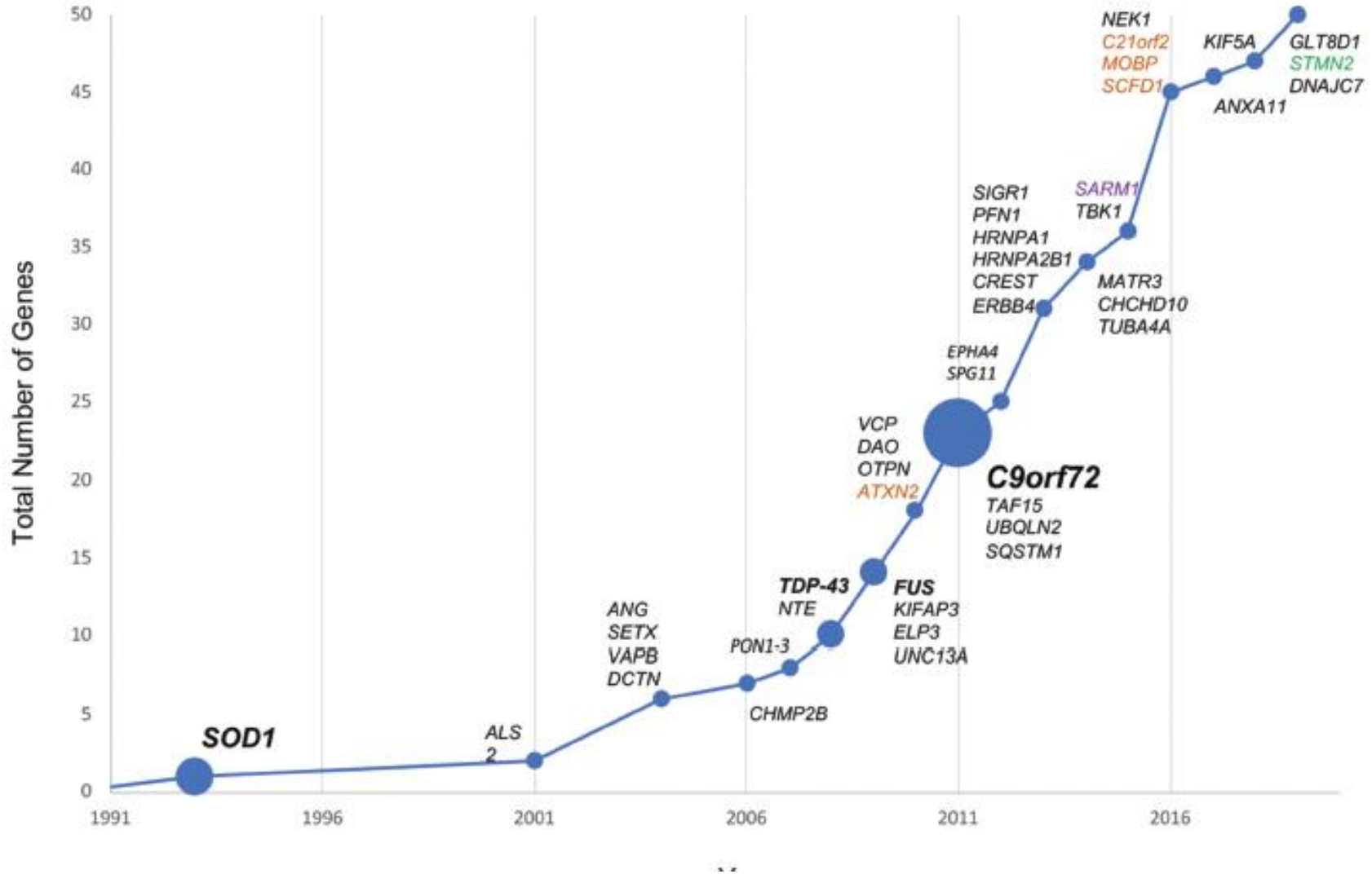
Rapid Growth in Gene Discovery



Quinn and Elman, Continuum, 2020

Penetrance – What is the chance that a genetic change causes ALS?

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Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital

ALS Causative Genes

SOD1

90% lifetime risk for ALS

C9orf72

50-90% lifetime risk of ALS or FTD

RISK ALLELES
One of multiple factors that may contribute to sporadic ALS

"gene-environment interaction"

ATXN2

~1% lifetime risk for ALS

3-4x higher than general population)

UNC13A polymorphism

~0.3% lifetime risk of ALS

1.1x higher than general population

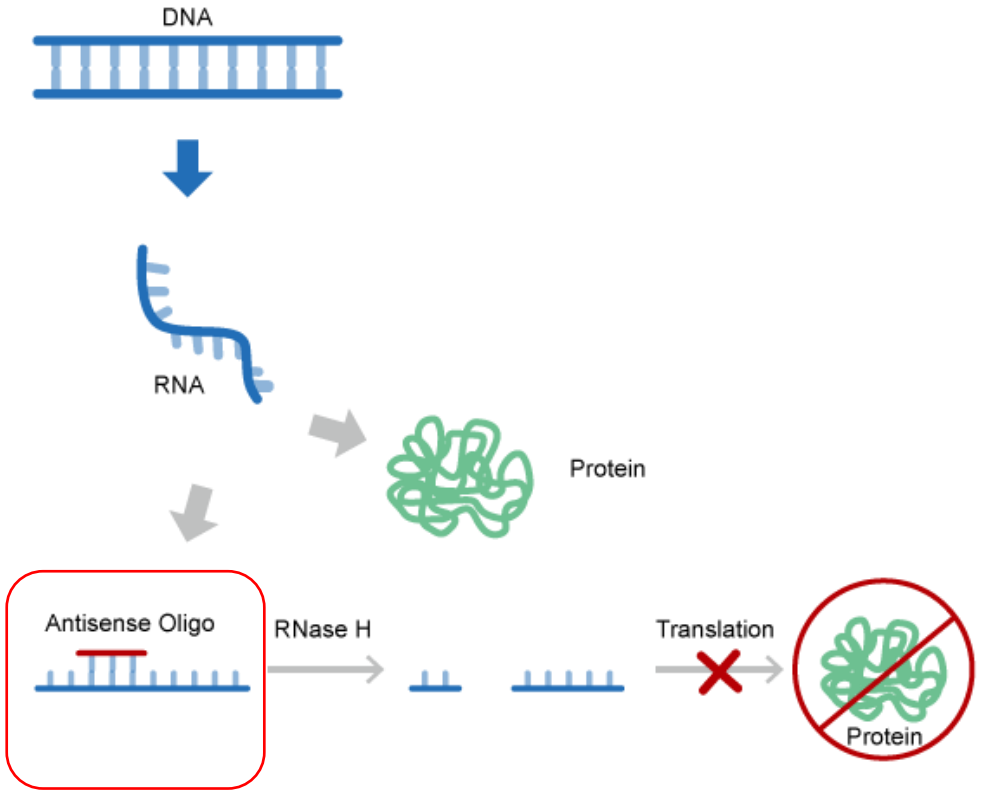
Precision Medicine in ALS

Tailor treatments to the underlying genetic causes of disease in an individual

- Familial ALS: Tofersen (Qalsody) approved for SOD1 ALS in April 2023
- Sporadic ALS: ALS risk alleles
  - Trials for ATXN2, STMN2, UNC13A

Antisense Oligonucleotides (ASO):

- Small pieces of DNA designed to bind to a specific RNA sequence -> destruction of that RNA and decreased levels of protein



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Could we start treating earlier?

Identifying who is at risk for ALS

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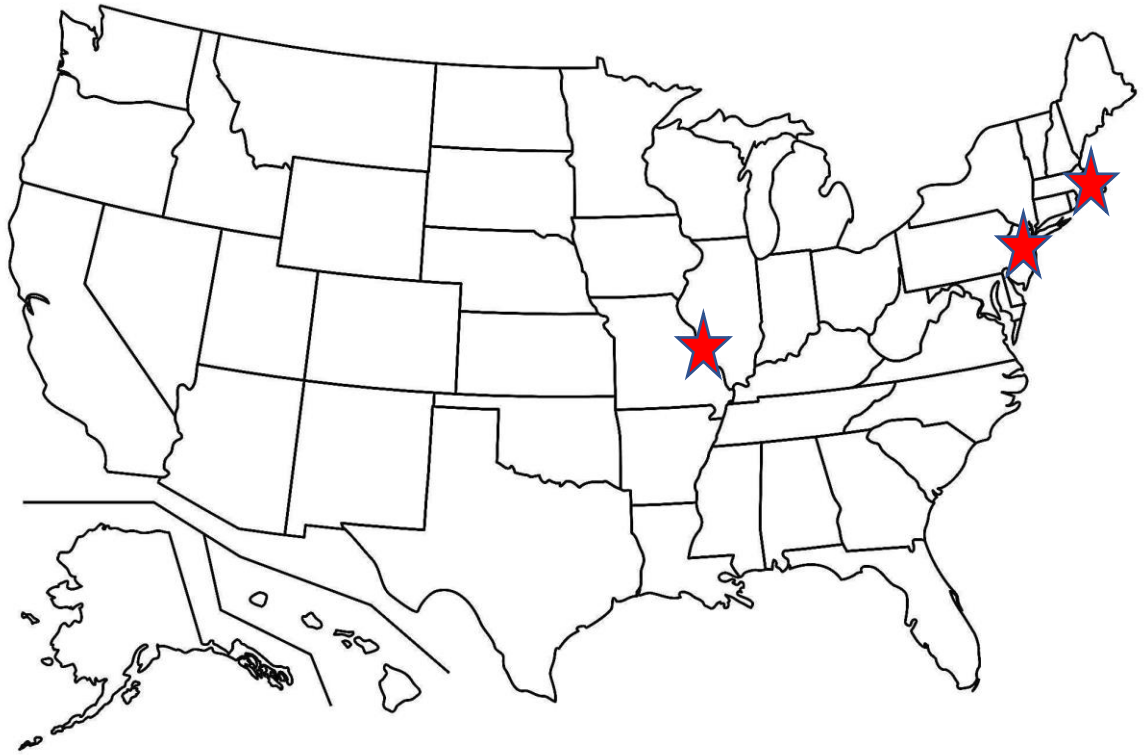
Family members of patients with genetic ALS/FTD

- Can perform genetic testing prior to onset of symptoms to identify those at risk
- Teaches us about ALS disease biology, offers possibility to prevent ALS



PREVENT ALS

Massachusetts General Hospital
Founding Member, Mass General Brigham

Washington University in St. Louis
University Advancement

Columbia

PREVENT ALS Study

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at Massachusetts General Hospital

	MGH DIALS	WashU DIALS	ALS Families	PREVENT ALS
Total Enrollment	241	46	204	491
Gene positive	121	20	106	247
C9orf72	91	15	58	164
SOD1	17	3	20	40
Multiple Variants	1	1	0	2
Rare variants	14	1	28	43
Gene negative	78	15	66	159
Non-Disclosure	31	8	20	59
Pending Genetics	11	2	12	25

Discovering the earliest changes in ALS

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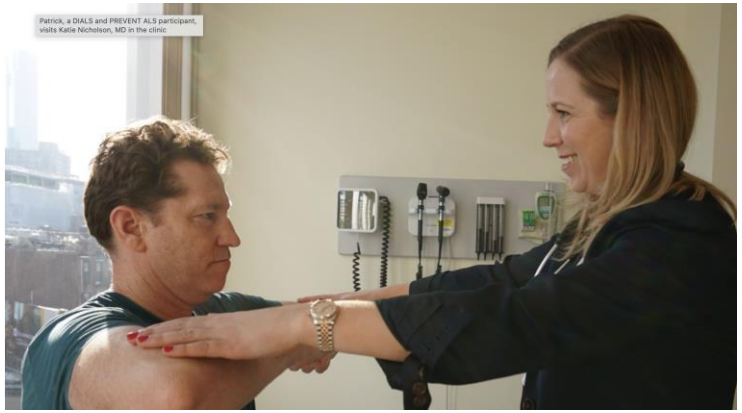
Genetic testing and counseling

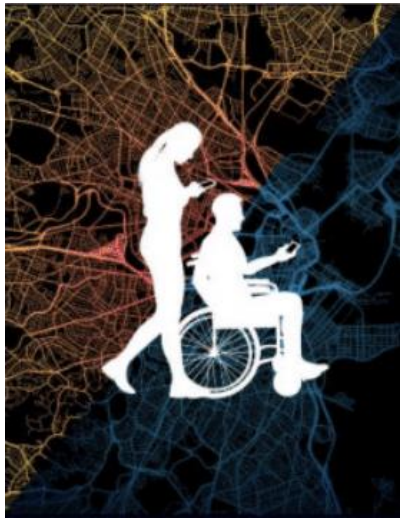
Cognitive Assessments



Neurologic examinations

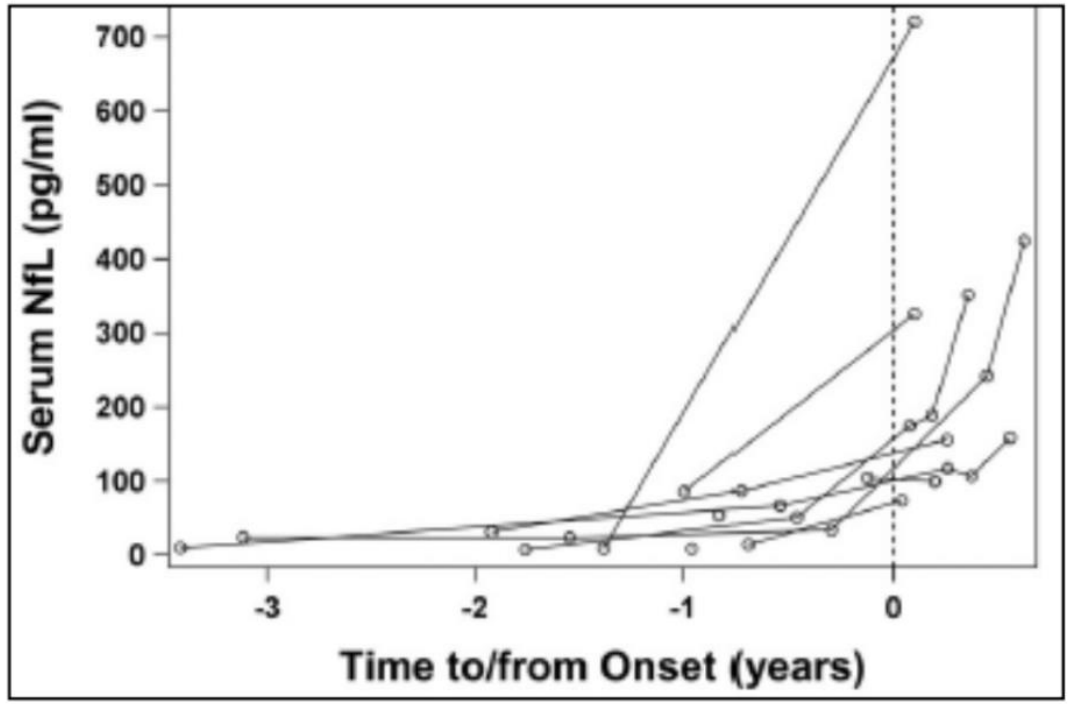
Biofluid/Tissue banking

Digital monitoring

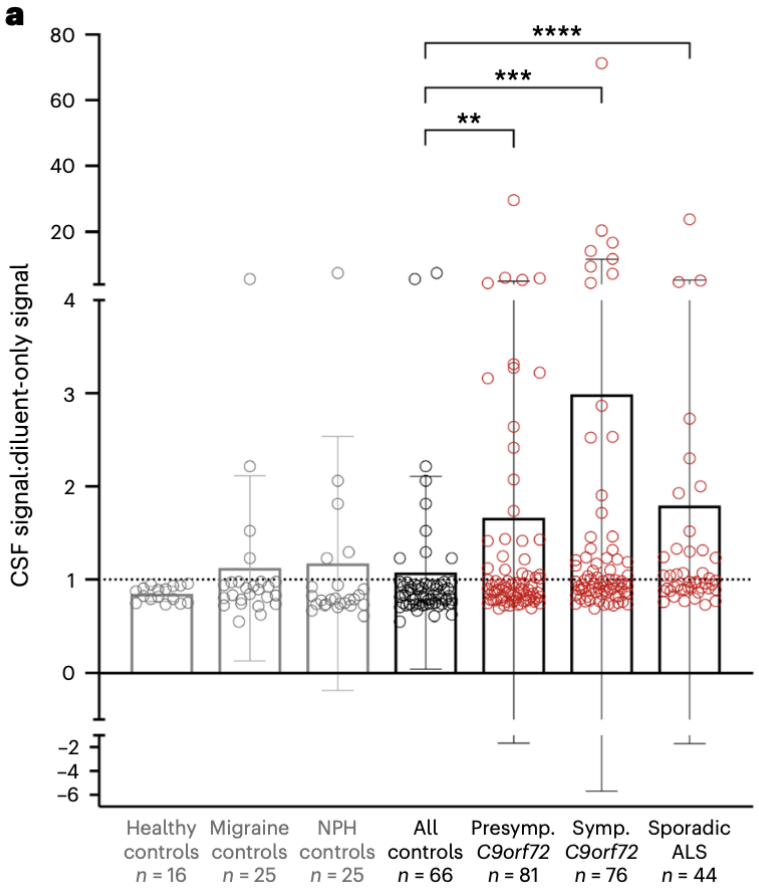


Electrophysiologic studies

“Biomarkers” to detect early or prodromal ALS



Benatar et. al. Annals of Neurology 2018



Irwin et al., 2024

Neurofilament Light Chain (NFL): marker of nerve injury, elevated 6-12 months prior to onset of ALS

“Cryptic exons” reflecting loss of TDP-43 function in ALS and asymptomatic C9orf72 carriers

ALS Prevention

ATLAS Trial: Asymptomatic SOD1 gene carriers without ALS

- Treat with tofersen (SOD1 antisense oligonucleotide) or Placebo
- Does treatment result in delay in developing ALS for people with rising neurofilament levels

How should we monitor and counsel people at genetic risk of ALS/FTD?

- Riluzole?
- Lifestyle modifications?