

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



Healey & AMG Center

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



Calico



The AMG Foundation

Patient Navigation

Central resource for people living with ALS



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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)



Allison Bulat



Genetics of ALS

Mark Garret, MD

Is ALS inherited?

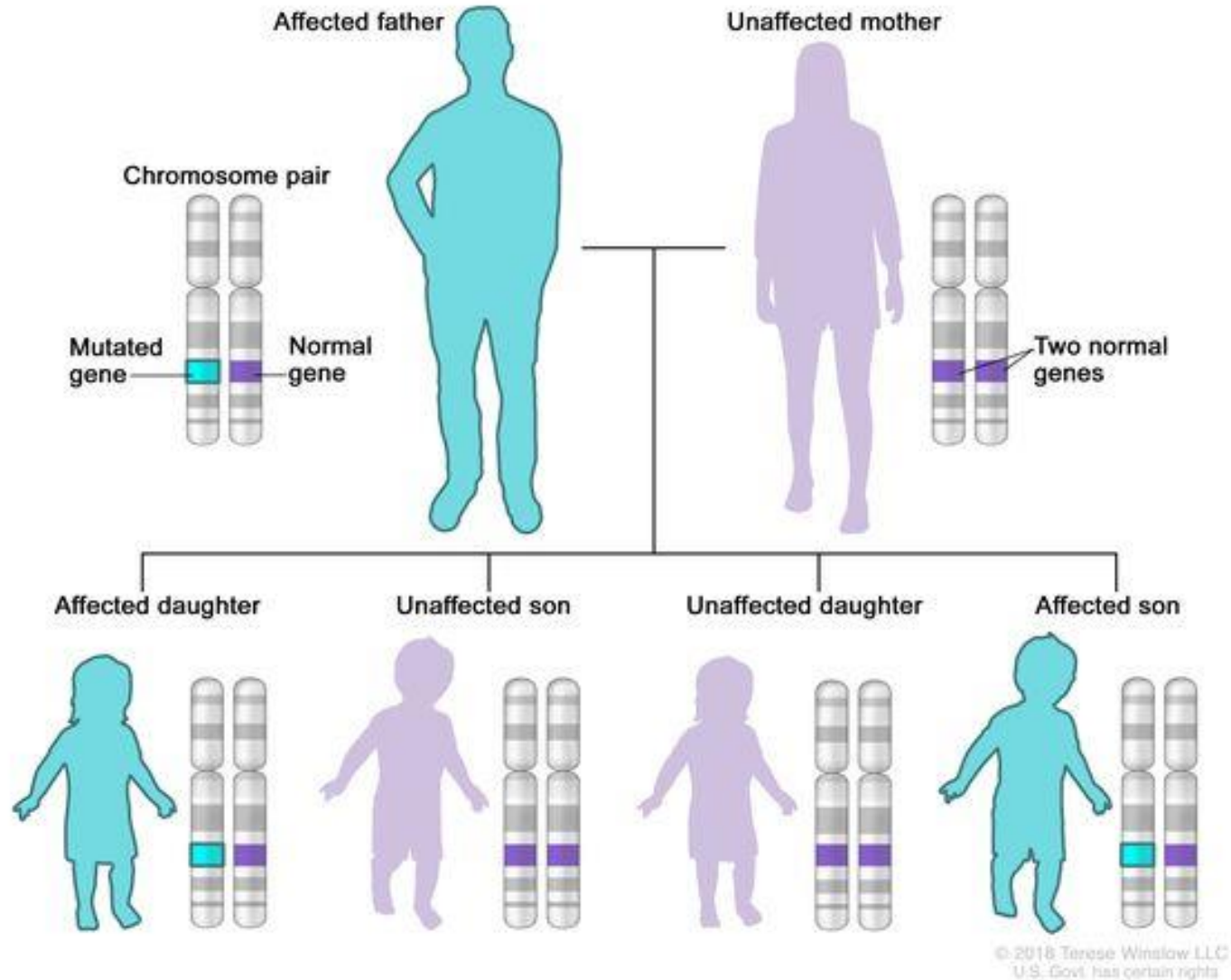
“Familial” or “Genetic” ALS

- 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



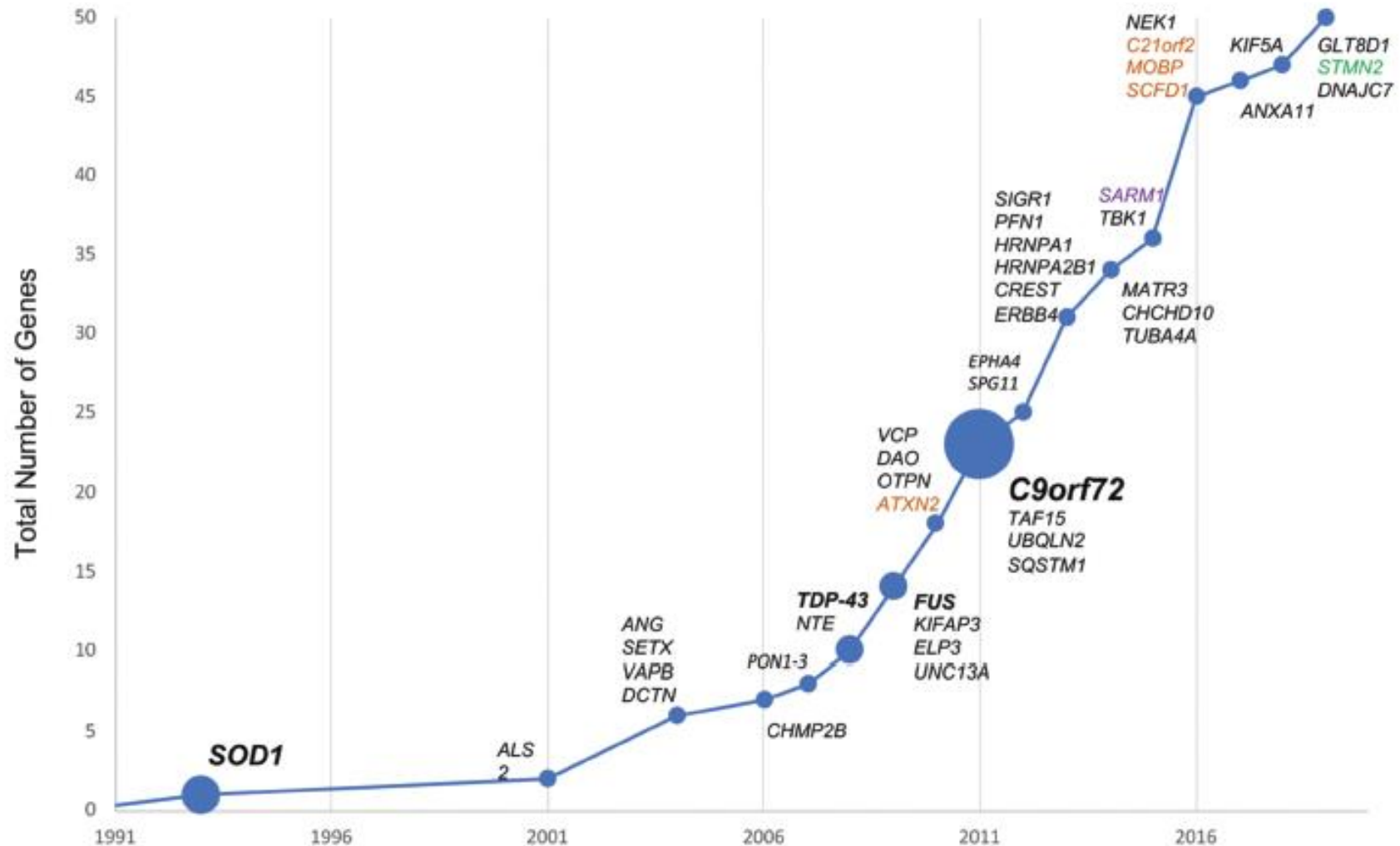
Autosomal Dominant Inheritance



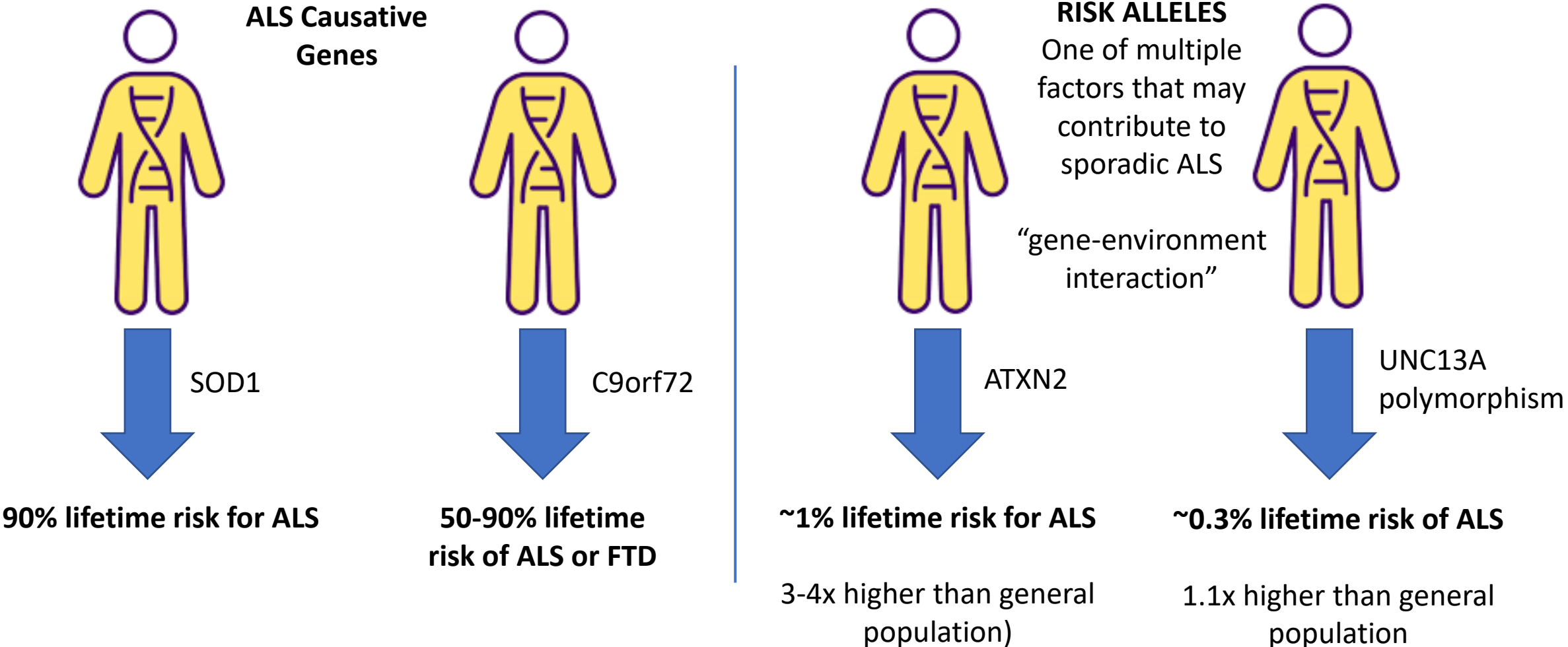
Dominant Inheritance:

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

Rapid Growth in Gene Discovery



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



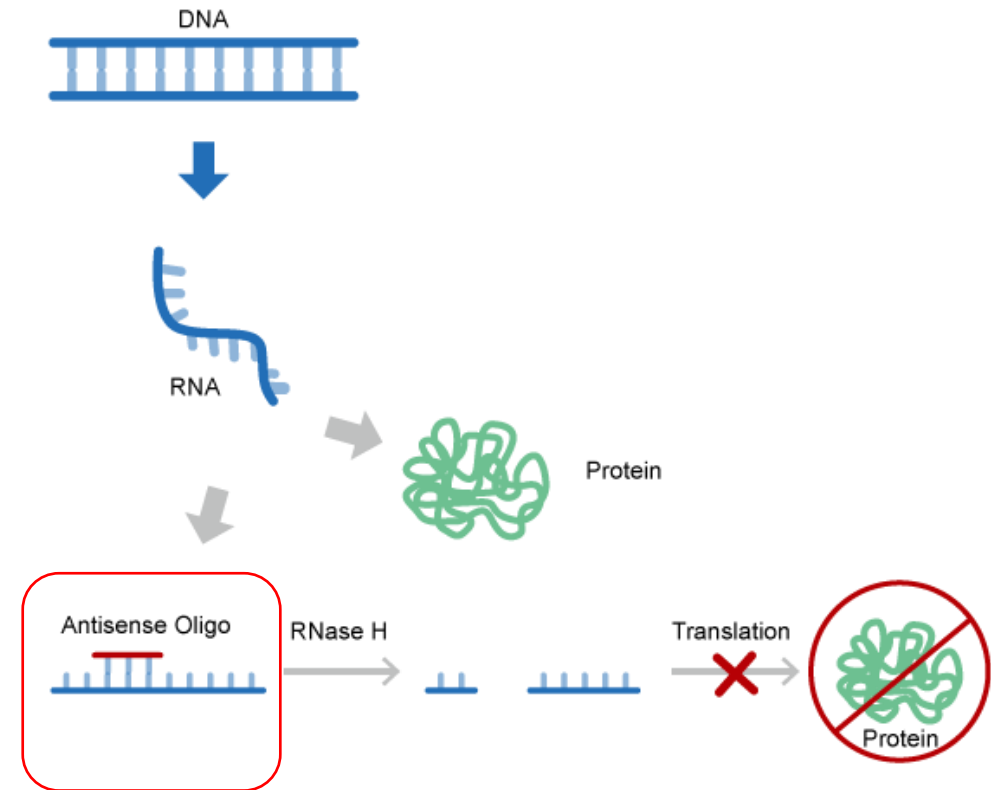
Precision Medicine in ALS

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



Could we start treating earlier?



Identifying who is at risk for ALS

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

	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



Genetic testing and counseling



Cognitive Assessments



Neurologic examinations



Biofluid/Tissue banking

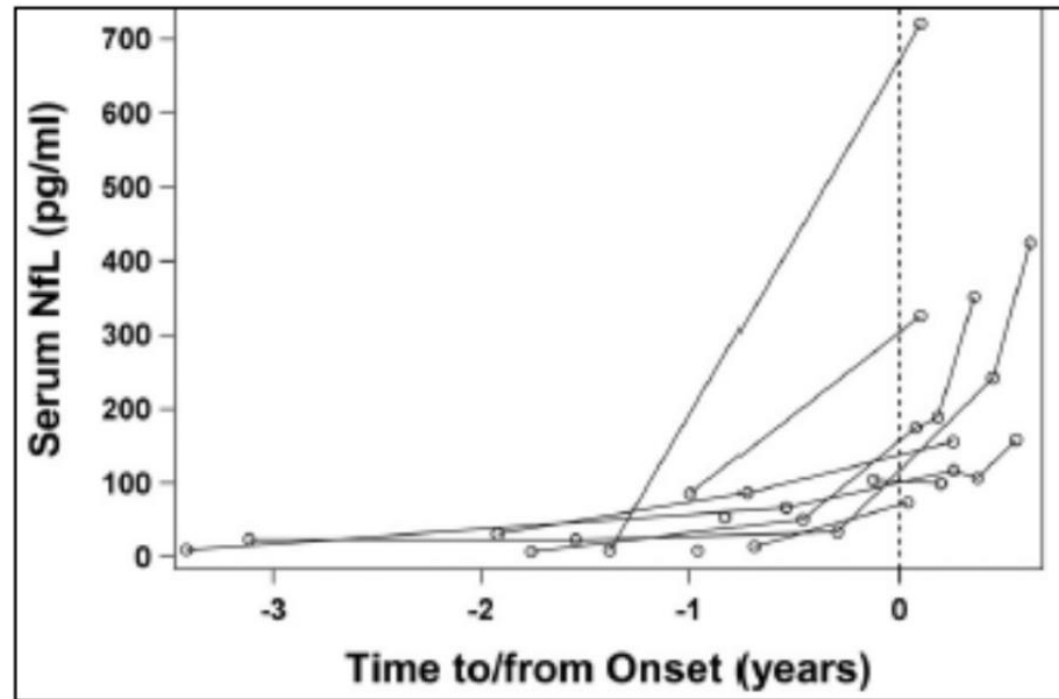


Digital monitoring



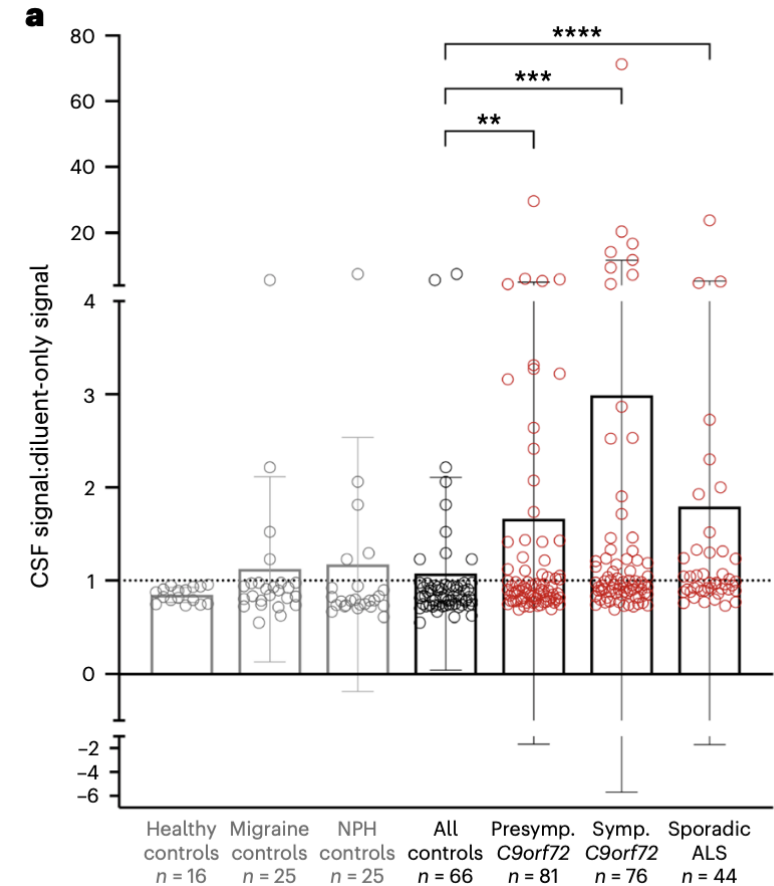
Electrophysiologic studies

“Biomarkers” to detect early or prodromal ALS



Benatar et. al. Annals of Neurology 2018

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



Irwin et al., 2024

“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?