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Patient Navigation – Central resource for people living with ALS

Phone: 833-425-8257 (HALT ALS)

E-mail: healeyalsplatform@mgh.harvard.edu

Register for webinars:

Upcoming Webinars (Thurs, 5:00- 5:30pm Eastern Time)

March 12 – CNM-Au8 EAP Update with Dr. Jinsy Andrews and Clene

March 19 – HEALEY ALS Platform Trial Regimen I Drug Science with Neurizon

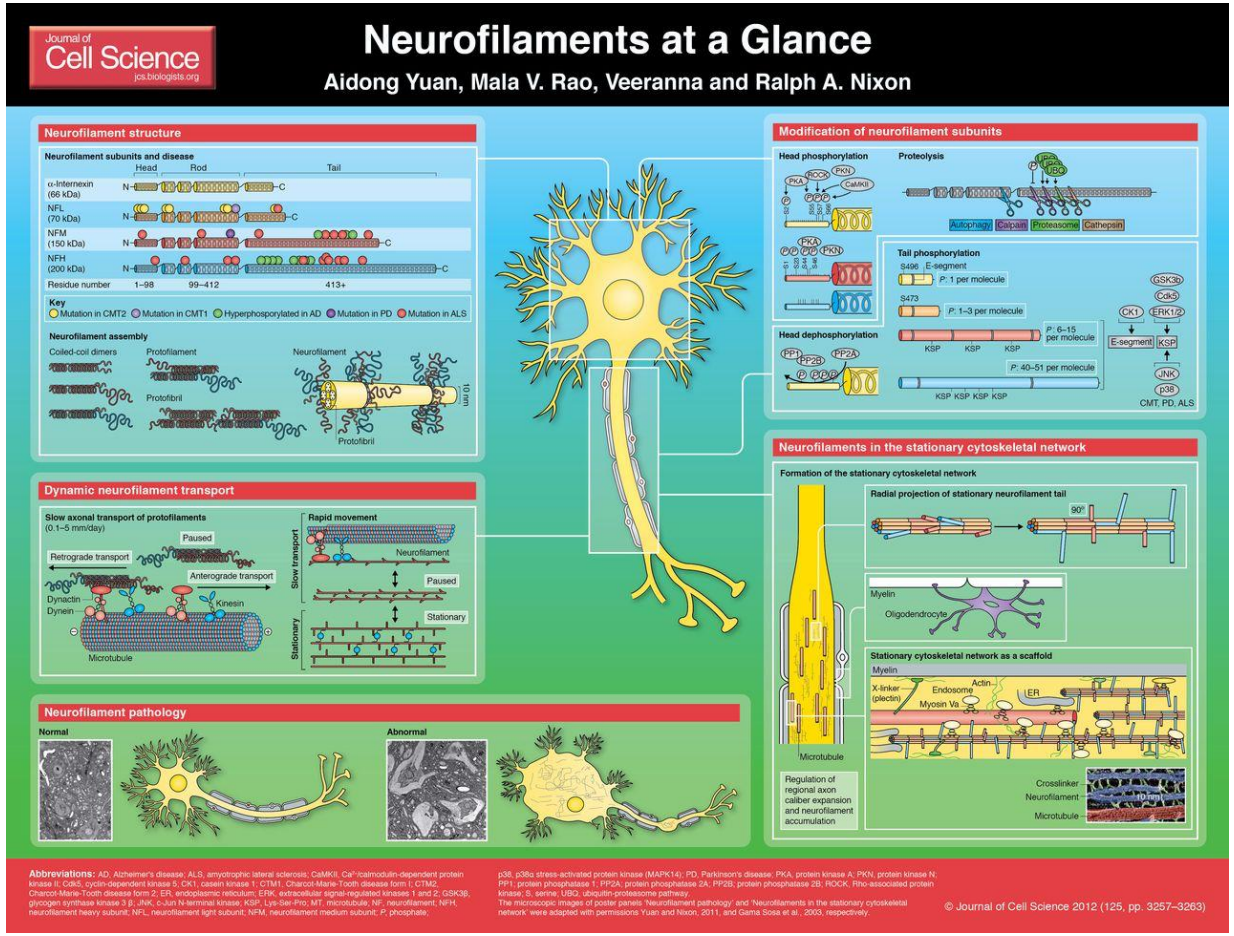
April 2 – Healey ALS MyMatch Update with Dr. Suma Babu

https://bit.ly/3r6Nd2L

Understanding Neurofilament (NfL) in ALS: What It Tells Us and How It Is Used in Clinical Trials

Clinician James Berry, MD, MPH
Biostatistician Jenny Wang, MS, PhD

Neurofilament is a structural protein in neurons and can be detected in CSF and blood

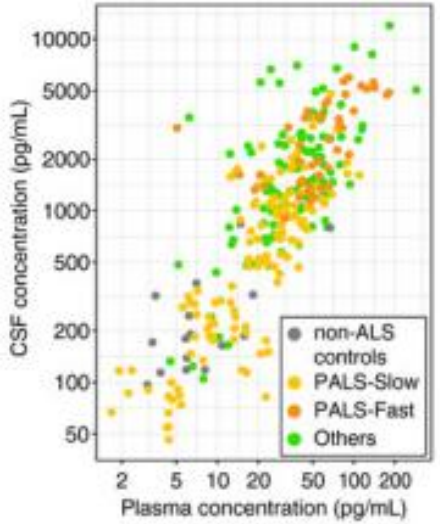


Provide structural support for the axon

3 polypeptide subunits

- Light-chain (NfL)
- Medium-chain (NfM)
- Heavy-chain (NfH)
  - Phosphorylation (pNfH)

Levels in blood (plasma) and CSF correlate highly



2020, ACTN, Huang

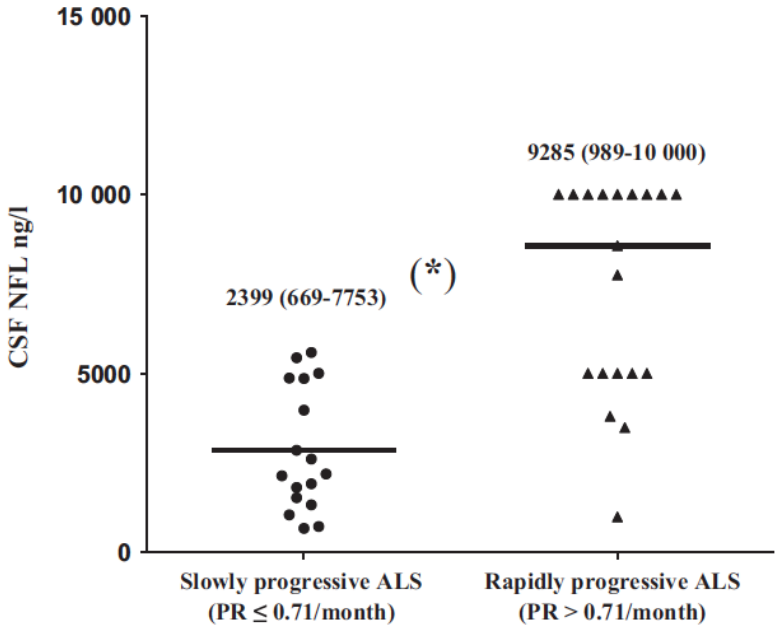
In ALS, NfL has Found Two Primary Uses as a Biomarker

- Prognosis
  - The level of NfL at baseline can suggest how quickly ALS will progress in the future
  - It is the best single predictor of progression

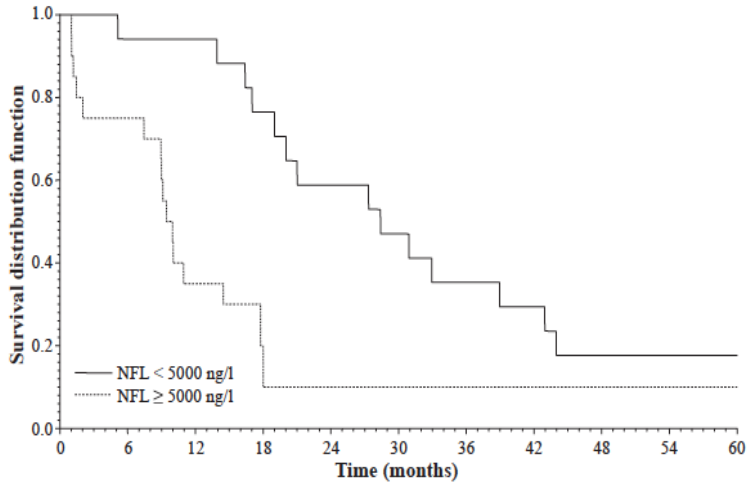
- Outcome Measure
  - In trials, NfL can be measured over time (longitudinally)
  - It is expected to be stable
  - If NfL decreases on an investigational product, it likely suggests the IP may slow disease

NfL is a Prognostic Biomarker in ALS

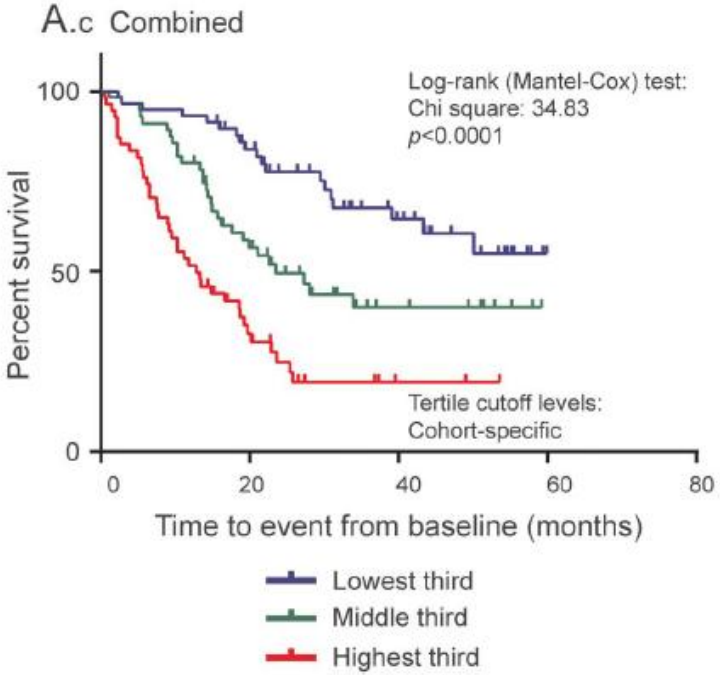
Lower CSF NFL Predicts Slower Progression



Lower CSF NFL Predicts Longer Survival



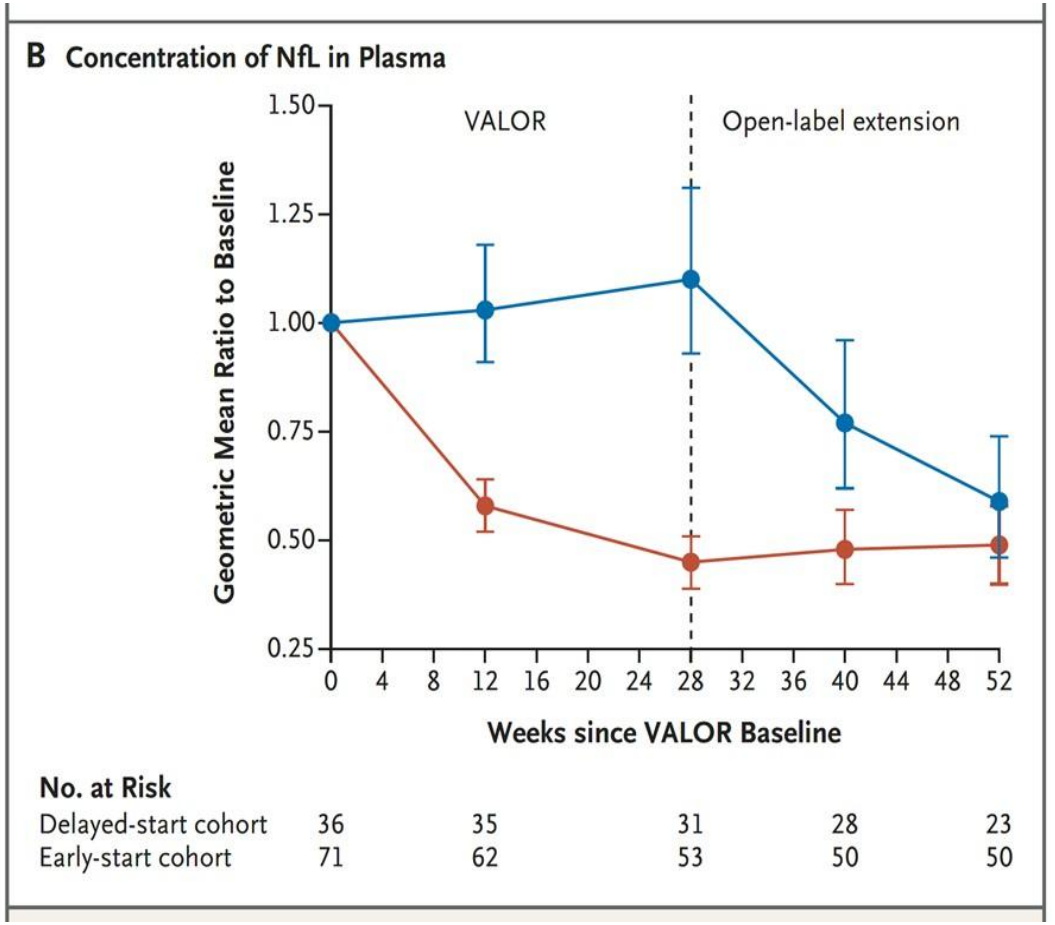
Lower Plasma NFL Predicts Longer Survival



2012 – Tortelli; 2014 – Tortelli; 2015 - Lu

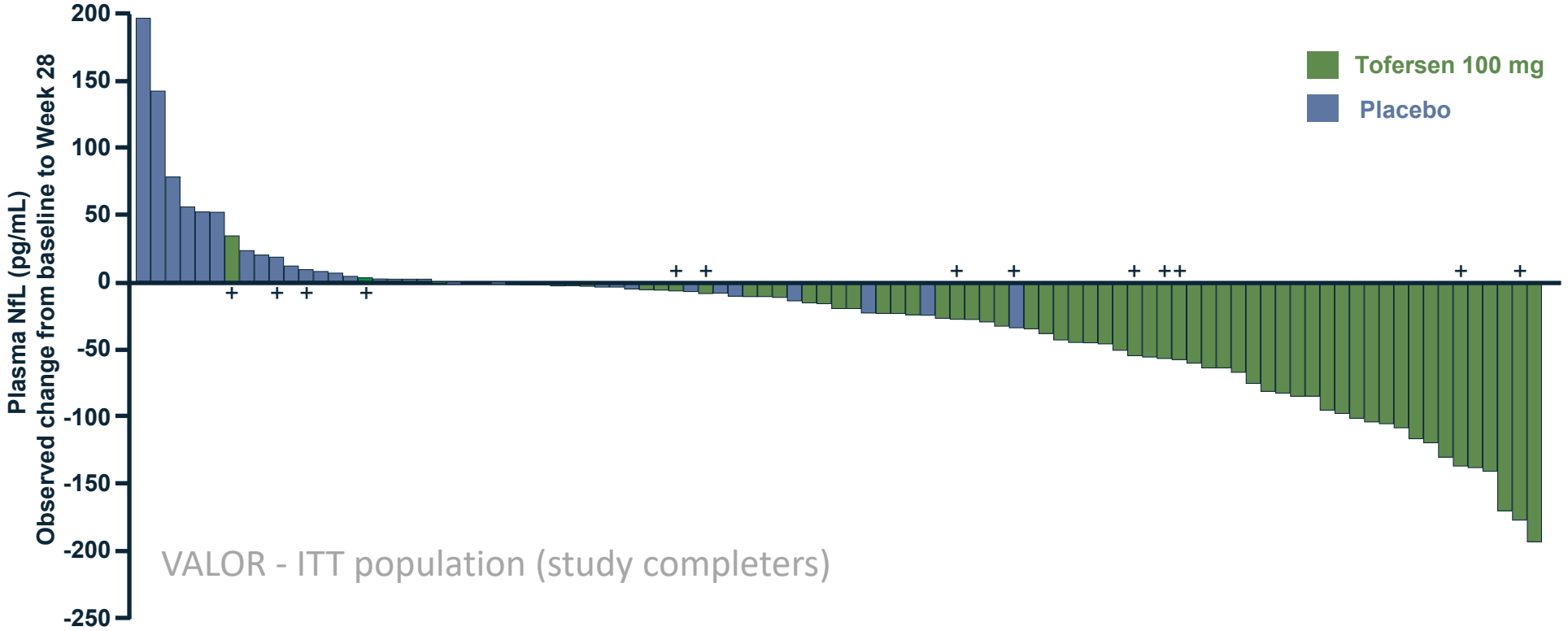
NfL as a Pharmacodynamic Biomarker

- Tofersen is used to treat ALS caused *SOD1* mutations.
- In the Phase 3 trial, NfL was measured over time. NfL was:
  - Stable in placebo (blue)
  - Reduced by ~60% in Tofersen
- After starting the open label extension (vertical dotted line):
  - NfL went down previously placebo
  - NfL stayed low in previous Tofersen



2022, NEJM, Miller

Individual Variability in NfL Response (Tofersen Trial)



Observed data are presented for only study completers with a valid NfL result at Day 169 or Day 197.
For completers with Day 197 data available, change from baseline at Day 197 is presented. For completers with missing Day 197 data, change from baseline at Day 169 is presented with +.
Values below limit of quantitation (BLQ) are set to half of lower limit of quantitation (LLOQ. 4.9 pg/mL) in calculations.

Today We will Review NfL and Clinical Data from Participants with ALS in Answer ALS and the HEALEY ALS Platform Trial

Answer ALS

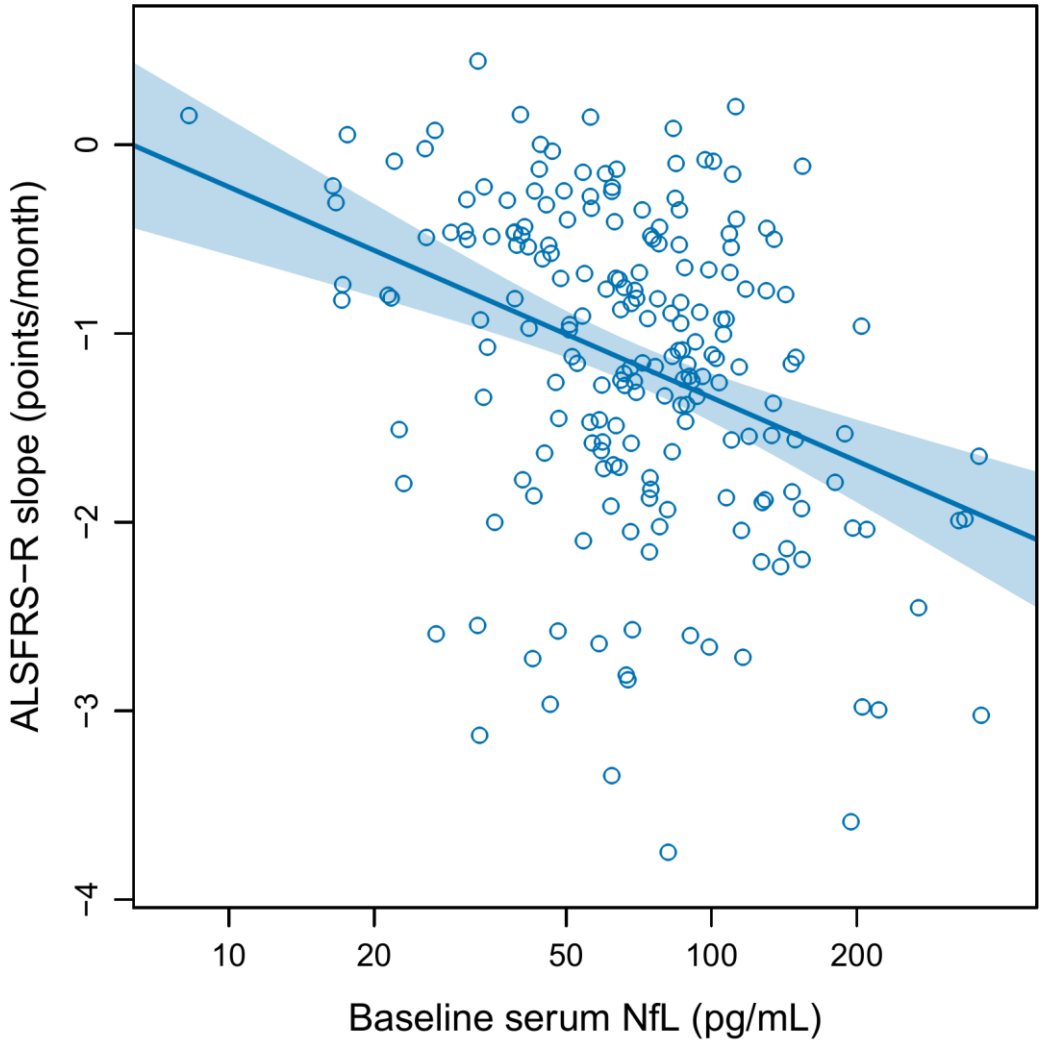
- Longitudinal observational study
- Enrolled 1000 participants, ~800 with ALS
- Collected clinical data, including ALSFRS-R
- Visits every 3 months for a year, though follow-up was variable
- NfL was analyzed on the Siemens platform

HEALEY ALS Platform Trial

- Clinical trial with multiple regimens occurring in parallel and serial
- 343 participants with ALS were included in the placebo group
- Visits every 2 months for 6 months
- NfL was analyzed on the Quanterix Simoa assay

NfL as a Prognostic Biomarker in the HEALEY ALS Platform Trial and Answer ALS

In the HEALEY ALS Platform Trial, NfL Predicts Rate of Functional Decline



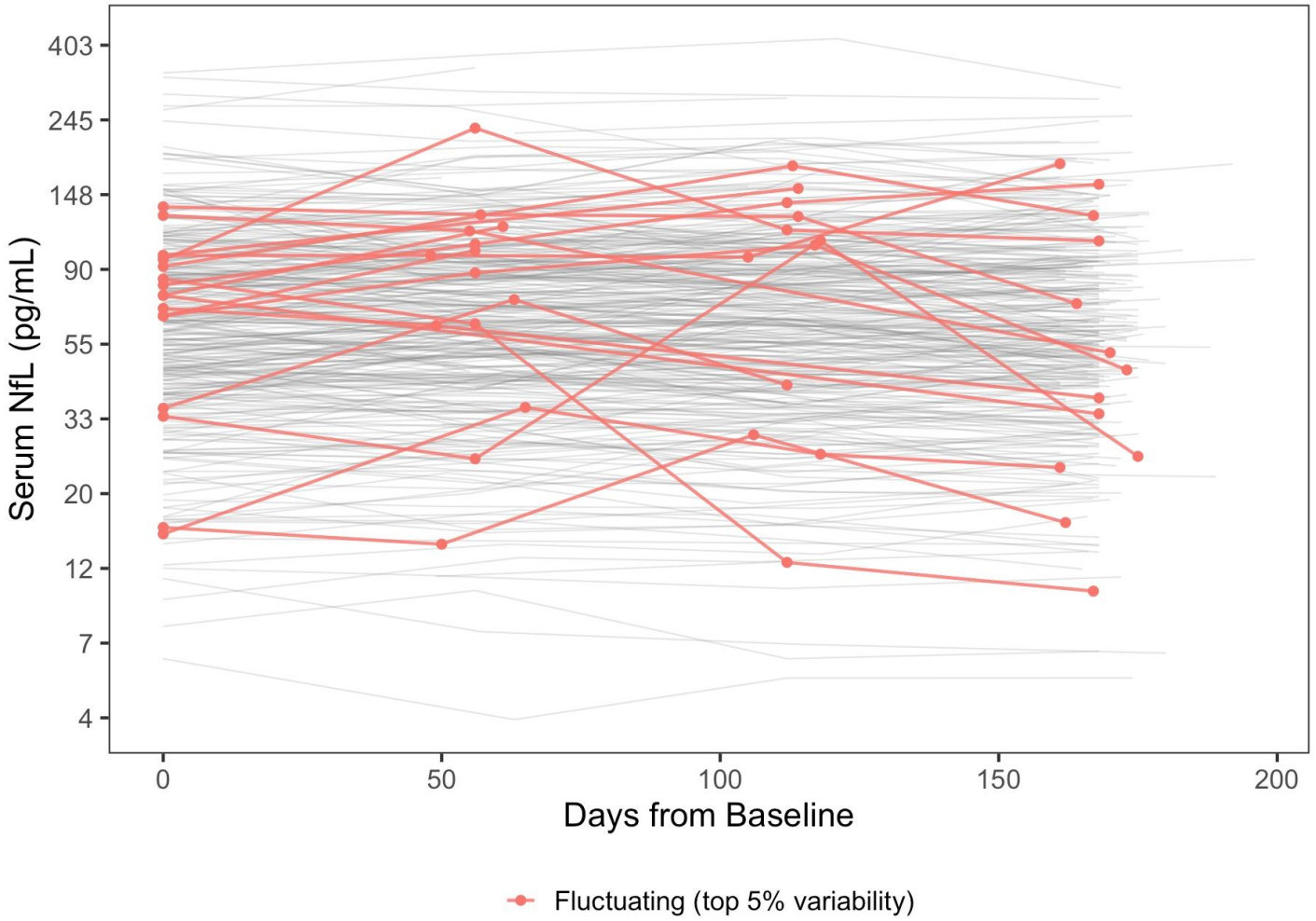
NfL as a Dynamic Trial Endpoint in the HEALEY ALS Platform Trial and Answer ALS

Individual NfL Trajectories
-Observation from the HEALEY ALS Platform Trial Placebo

Among all with at least two NfL (N=331) measurements:

95% (N=314) show stable NfL levels, with a median within-person variation at $(-11\%, +12.3\%)$;

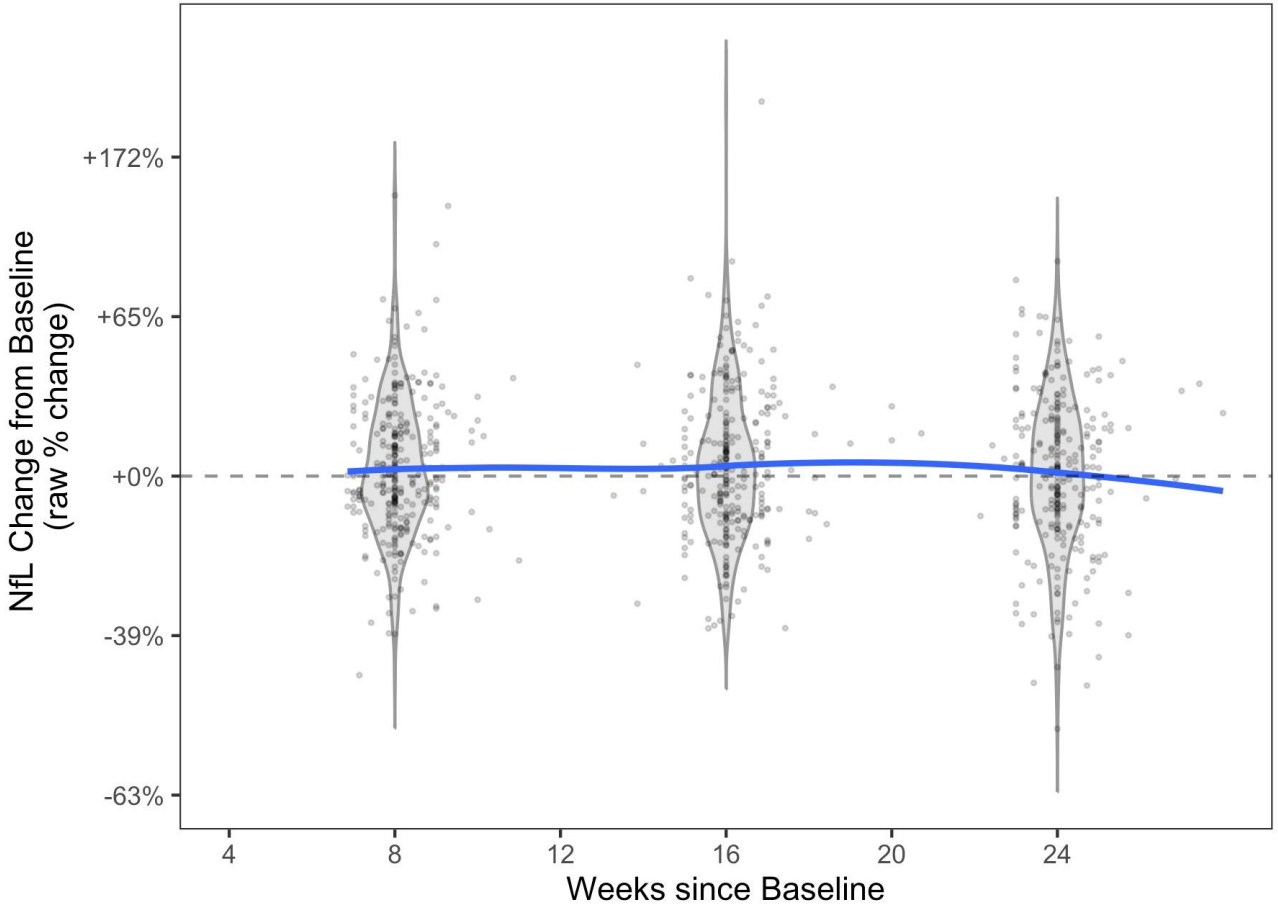
5% (N=17) show more variable NfL levels, with a median within-person variation at $(-29.0\%, +40.0\%)$. Among them, 70.6% (N=12) had reached $+40.0\%$ change in at least one test; 35.3% (N=6) had reached -29.0% change in at least one test.



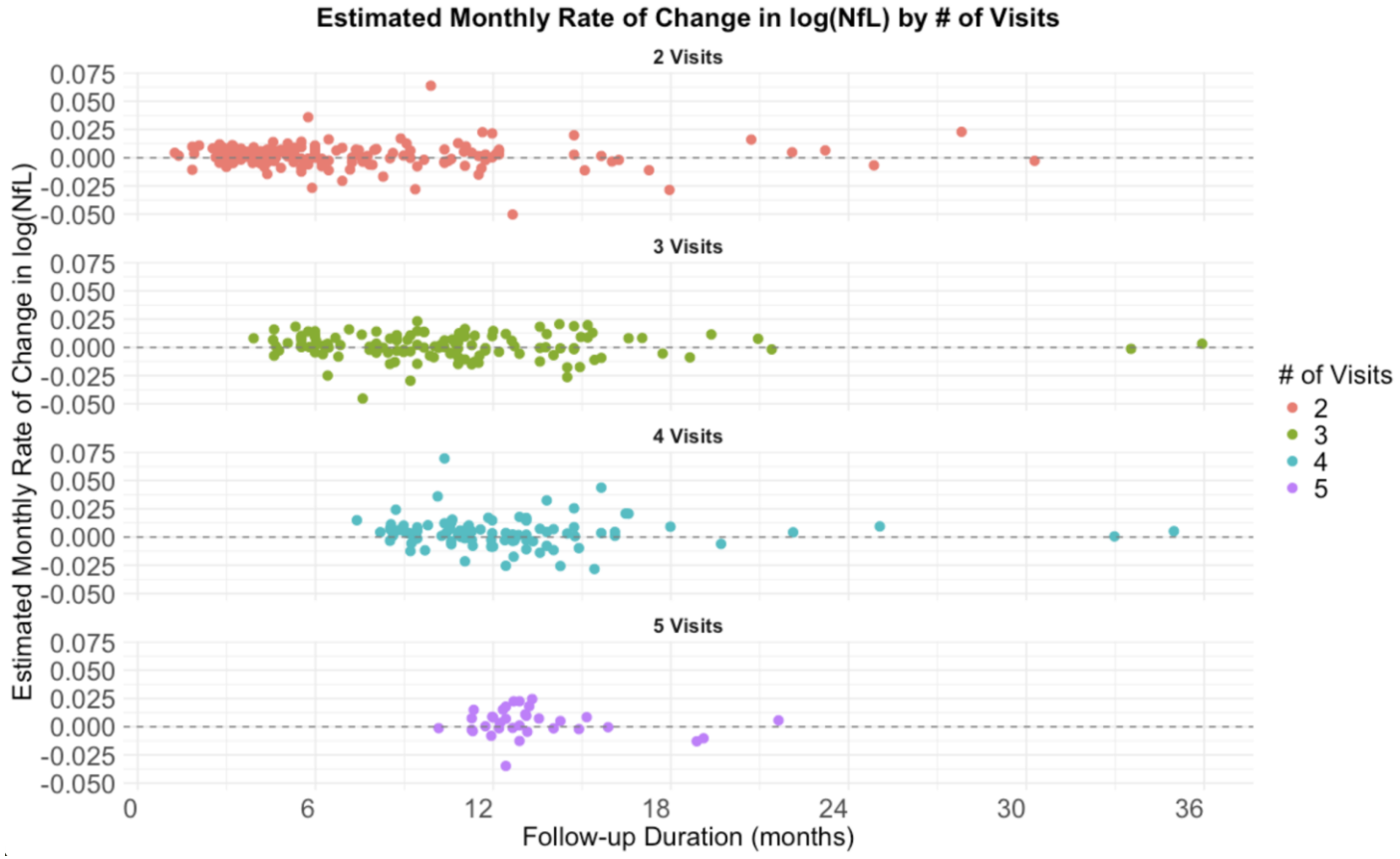
NfL Remains Stable Over Time (Though Variability Exists)

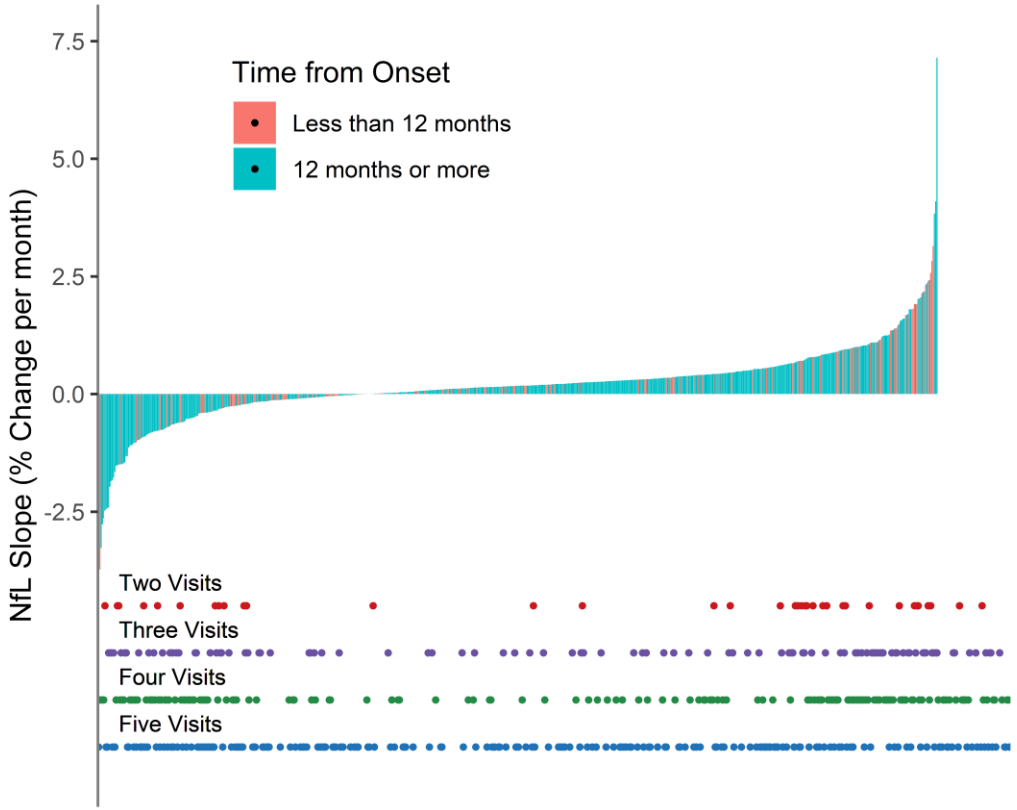
-Observation from HEALEY ALS Platform Trial Placebo

- Each point represents an individual participant's percent of change in NfL from baseline at a given visit;
- Violin plots show the distribution of change at each visit (up to Weeks 24);
- The blue line represents a smoothed trend across time;
- The dashed horizontal line indicates no change from baseline (0%).

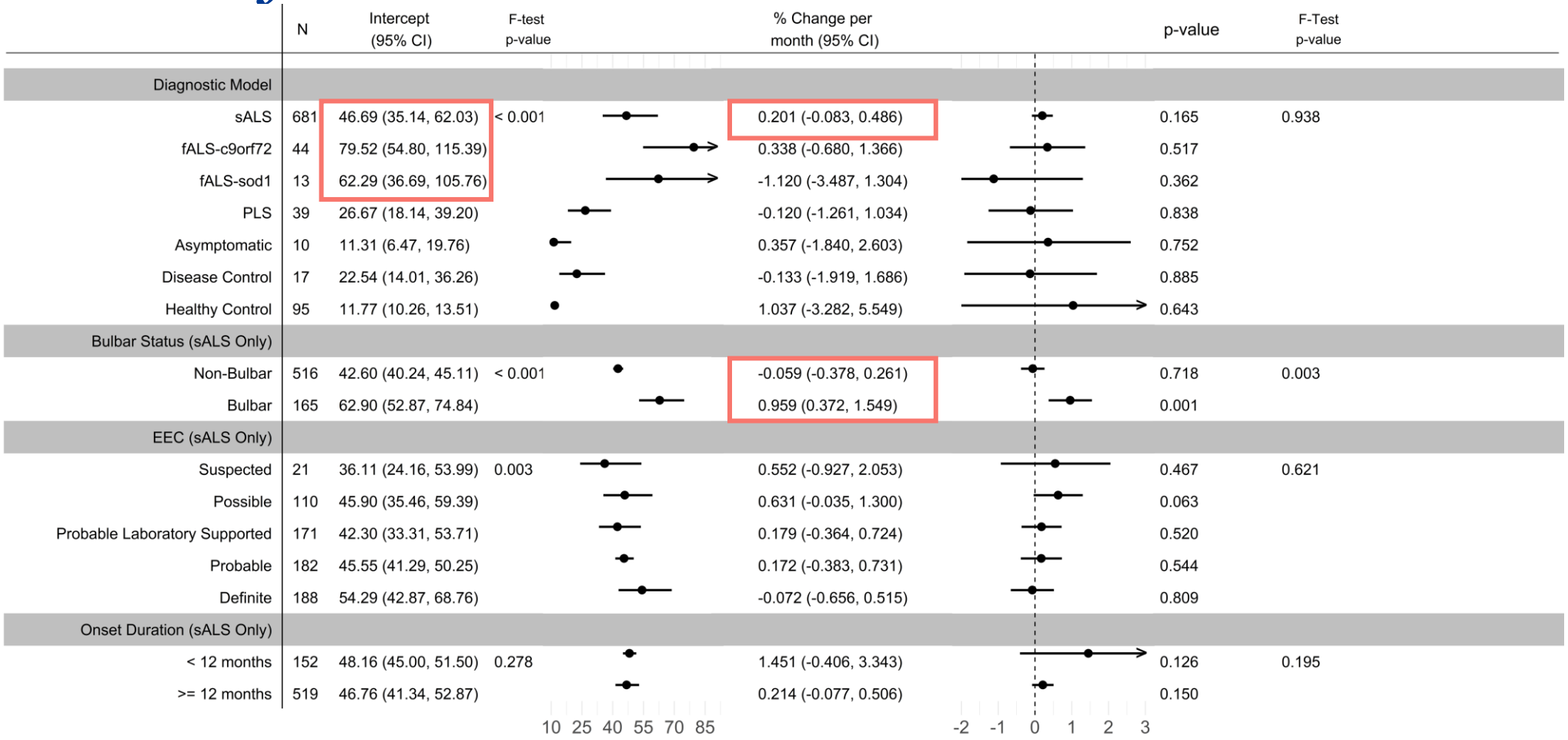


Measurement Frequency and Duration Matter
- Observation from Answer ALS





Predictors of the NfL Trajectories
- *Observation from Answer ALS*



	N	Intercept (95% CI)	F-test p-value	% Change per month (95% CI)	p-value	F-Test p-value
Diagnostic Model						
sALS	681	46.69 (35.14, 62.03)	< 0.001	0.201 (-0.083, 0.486)	0.165	0.938
fALS-c9orf72	44	79.52 (54.80, 115.39)		0.338 (-0.680, 1.366)	0.517	
fALS-sod1	13	62.29 (36.69, 105.76)		-1.120 (-3.487, 1.304)	0.362	
PLS	39	26.67 (18.14, 39.20)		-0.120 (-1.261, 1.034)	0.838	
Asymptomatic	10	11.31 (6.47, 19.76)		0.357 (-1.840, 2.603)	0.752	
Disease Control	17	22.54 (14.01, 36.26)		-0.133 (-1.919, 1.686)	0.885	
Healthy Control	95	11.77 (10.26, 13.51)		1.037 (-3.282, 5.549)	0.643	
Bulbar Status (sALS Only)						
Non-Bulbar	516	42.60 (40.24, 45.11)	< 0.001	-0.059 (-0.378, 0.261)	0.718	0.003
Bulbar	165	62.90 (52.87, 74.84)		0.959 (0.372, 1.549)	0.001	
EEC (sALS Only)						
Suspected	21	36.11 (24.16, 53.99)	0.003	0.552 (-0.927, 2.053)	0.467	0.621
Possible	110	45.90 (35.46, 59.39)		0.631 (-0.035, 1.300)	0.063	
Probable Laboratory Supported	171	42.30 (33.31, 53.71)		0.179 (-0.364, 0.724)	0.520	
Probable	182	45.55 (41.29, 50.25)		0.172 (-0.383, 0.731)	0.544	
Definite	188	54.29 (42.87, 68.76)		-0.072 (-0.656, 0.515)	0.809	
Onset Duration (sALS Only)						
< 12 months	152	48.16 (45.00, 51.50)	0.278	1.451 (-0.406, 3.343)	0.126	0.195
>= 12 months	519	46.76 (41.34, 52.87)		0.214 (-0.077, 0.506)	0.150	

Massachusetts General Hospital
Founding Member, Mass General Brigham

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

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