Biomarkers in Clinical Trials

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NINDS Clinical Trials Methods Course

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Disclosures

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  - NIH, CDC, DOD, MDA, ALSA, Target ALS
- **Industry Trials**
  - ALS: Orphazyme, Biogen
  - MG: Alexion, UCB Pharma
- **Consulting**
  - MG: UCB Pharma
  - ALS: Denali, MT Pharma, AveXis, Biogen, Prilenia

Outline

- Challenges that biomarkers may address
- Biomarkers
  - Introduction
  - Discovery and validation
  - Context of use
- Leading ALS biofluid biomarker candidates
  - Prognostic utility
  - Potential pharmacodynamic utility
  - Relevance to disease prevention

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Challenges …
(that may be addressed by biomarkers)

- Translation
  - Selection of drugs from pre-clinical models
- Etiological and biological heterogeneity
  - Identifying (subset of) patients most likely to benefit from an experimental therapeutic
- Signal detection
  - Clinically meaningful change vs. biological effect
- Phenotypic heterogeneity
  - Distinguishing the therapeutic ‘signal’ from the ‘noise’ of natural variability

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Biomarkers: Good, Bad & Ugly

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- Plethora of candidate biomarkers

Example: ALS

Biological Fluid-Based	Neuroimaging	Neurophysiology
Neurofilament heavy	DTI	MUNE
Neurofilament light	MRS	MUNIX
Urinary $p75NTR^{ECD}$	VBM	CMAP
CSF SOD1	fMRI	EIM
CSF Poly(GP)		TMS

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- Very few that are useful in clinical trials?

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- Discovery vs. validation
- Failure to appreciate nuance of developing biomarkers that are “fit for purpose”

Biomarkers: Good, Bad & Ugly

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- Very few that are useful in clinical trials?

WHY?

- Discovery vs. validation
- Failure to appreciate nuance of developing biomarkers that are “fit for purpose”
- Surrogacy

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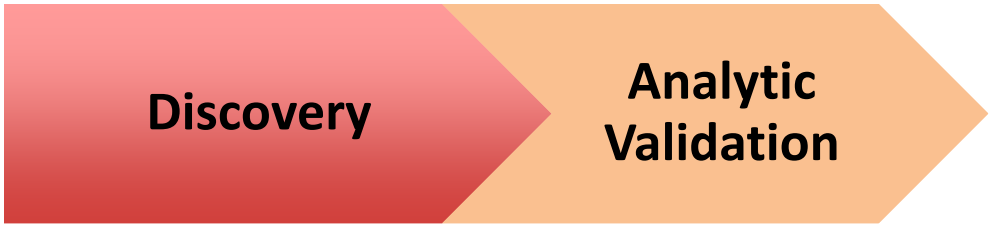
Biomarker Development Process: Discovery and Validation

Discovery

- Establish proof of concept
- Clinical samples of convenience
- Begin defining context of use

Biomarker Development Process: Discovery and Validation



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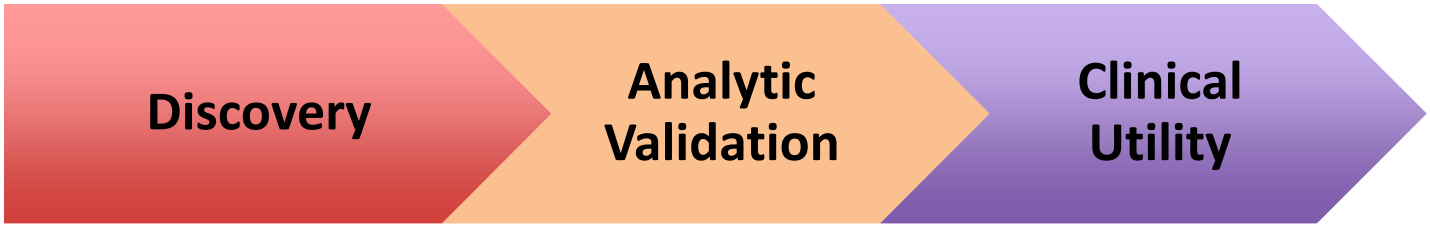
- Begin defining context of use

- Establish assay performance characteristics
- Evaluate impact of potential confounding factors
- Refine context of use

Biomarker Development Process: Discovery and Validation



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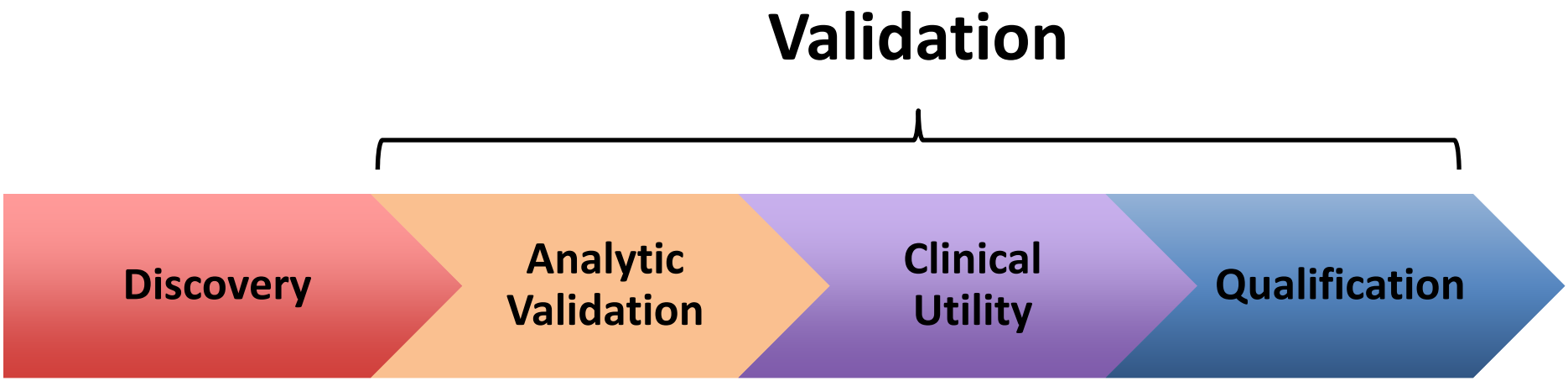
- Large, carefully-defined clinical cohort
- Well-defined SOPs
- Establish intended clinical use

Biomarker Development Process: Discovery and Validation



Discovery

- Establish proof of concept
- Clinical samples of convenience
- Begin defining context of use

Analytic Validation

- Establish assay performance characteristics
- Evaluate impact of potential confounding factors
- Refine context of use

Clinical Utility

- Large, carefully-defined clinical cohort
- Well-defined SOPs
- Establish intended clinical use

Qualification

- Demonstrated clinical utility
- Written context of use
- FDA review for qualification

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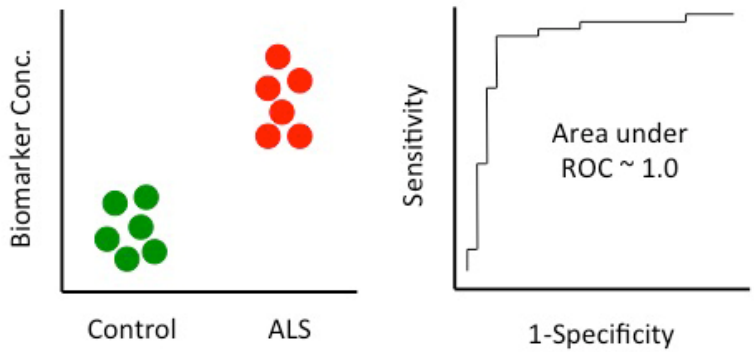
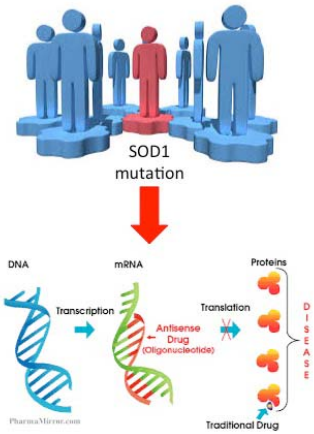
Biomarker Context of Use

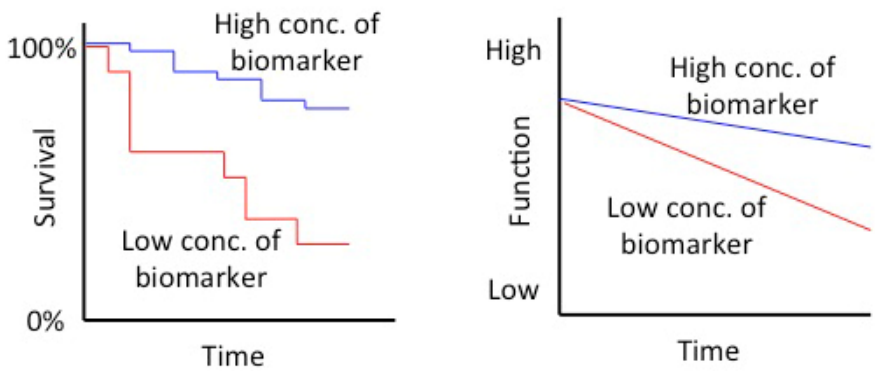
Diagnostic



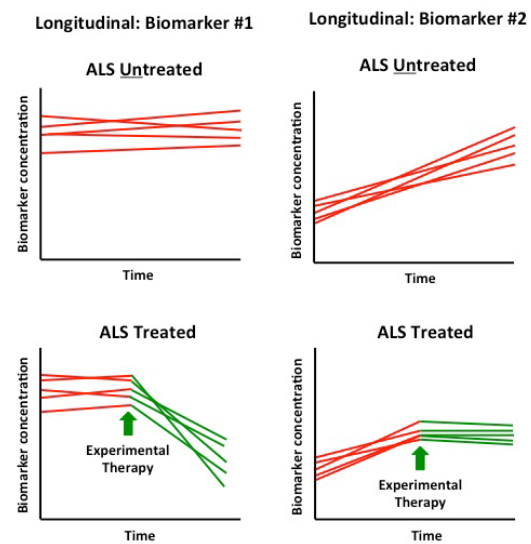
Predictive



Prognostic



Pharmaco-dynamic



Biomarker Context of Use

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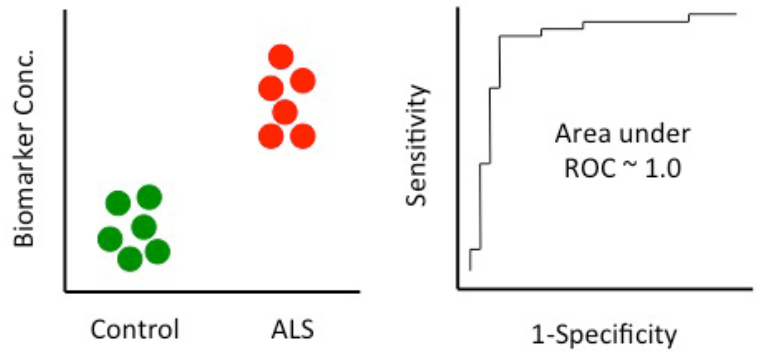

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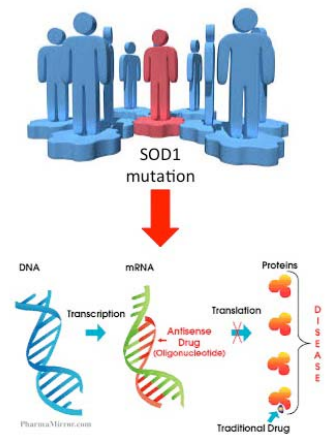
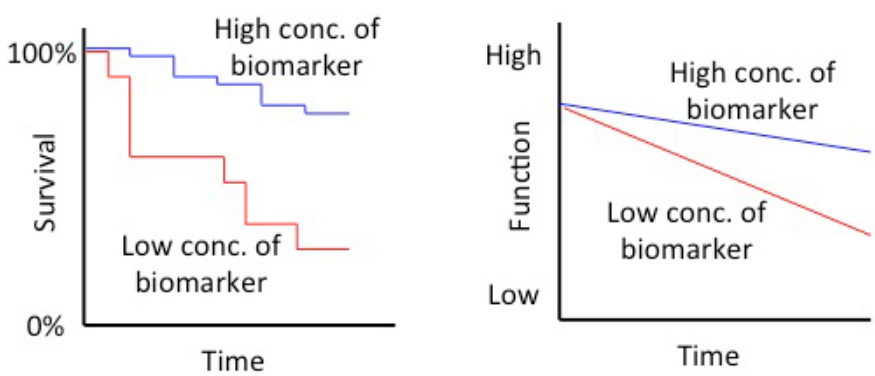


Prognostic



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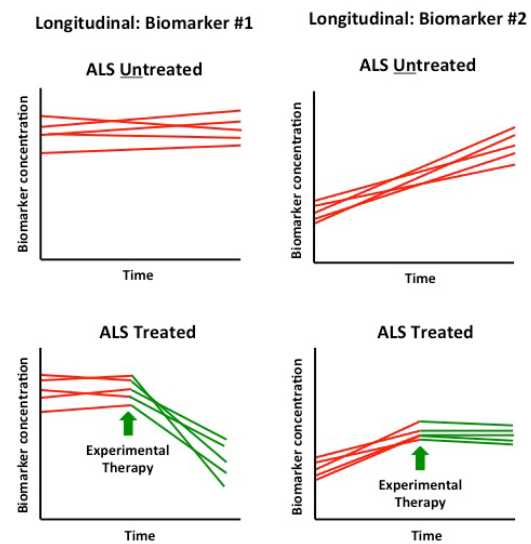

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Lead Biological Fluid Biomarkers

Biomarker Candidate	Possible Context of Use
Serum and CSF NfL	Prognostic and pharmacodynamic
Serum and CSF pNfH	Prognostic and pharmacodynamic
Urinary $p75^{ECD}$	Prognostic, disease progression and pharmacodynamic
CSF and PBMC poly(GP)	Pharmacodynamic

Assay Performance / Analytics

	$p75^{ECD}$	NfL	pNfH
Matrices	Urine	Blood, CSF	Blood, CSF
Platform	Sandwich ELISA	Simoa (Uman Abs)	Simoa
Analytic sensitivity	70pg/ml	0.0174 pg/ml	0.663 pg/ml
Dynamic range	70pg/ml – 2.5ng/ml	0-2,000 pg/ml	0-8,400 pg/ml
Confounds	• Renal failure • Diabetes • Neuropathy	• Other causes of axonal injury	• Other causes of axonal injury • ? Immune response
Normal range	≤ 2.6ng/mg creatinine (±0.96)	Blood: ≤ 6.6 pg/ml CSF: ≤ 2,467 pg/ml	Blood: ≤ 29 pg/ml CSF: ≤ 24,406 pg/ml
Assay reliability Intra-assay COV Inter-assay COV	 ~7% ~13%	 ~7% ~5%	 ~5% ~10%
Other	Stable at RT, 4°C and freeze-thaw cycles No diurnal Δ	Stable at RT, 4°C, -80°C, and freeze-thaw cycles	Stable at RT, 4°C, -80°C, and freeze-thaw cycles

Baseline Characteristics		ALS/FTD (N=225)	PMA (N=11)	PLS (N=10)
Age (years)	Mean ± SD	60 ± 11.8	56.8 ± 11.6	58.8 ± 11.1
Male	N (%)	130 (58%)	8 (73%)	9 (45%)
Genotype	*C9orf72*	27 (12%)	0	0
Years Since Onset	Median (IQR)	1.8 (1.0-3.2)	2.4 (1.7-9.0)	7.9 (3.8-11.6)
Years Since Dx	Median (IQR)	0.7 (0.3-1.6)	1.0 (0.6-4.3)	2.5 (1.5-5.5)
ALSFRS-R	Mean ± SD	34.6 ± 7.5	33.5 ± 8.5	35.2 ± 8.1
ΔFRS	Mean ± SD	0.62 ± 0.65	0.34 ± 0.36	0.17 ± 0.12
ALSFRS-R Slope	Mean ± SD	-0.65 ±0.65	-0.57 ±0.34	-0.09 ±0.46
# of collections	Median (range)	3 (2-5)	3 (2-5)	3 (2-5)
F/U duration (yrs)	Median (range)	0.8 (0.3-1.9)	0.6 (0.5-1.5)	1.0 (0.8-2.0)

Longitudinal subset: ALS (n=106), PMA (n-3), PLS (n=4)

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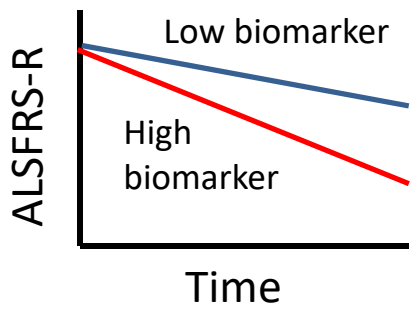
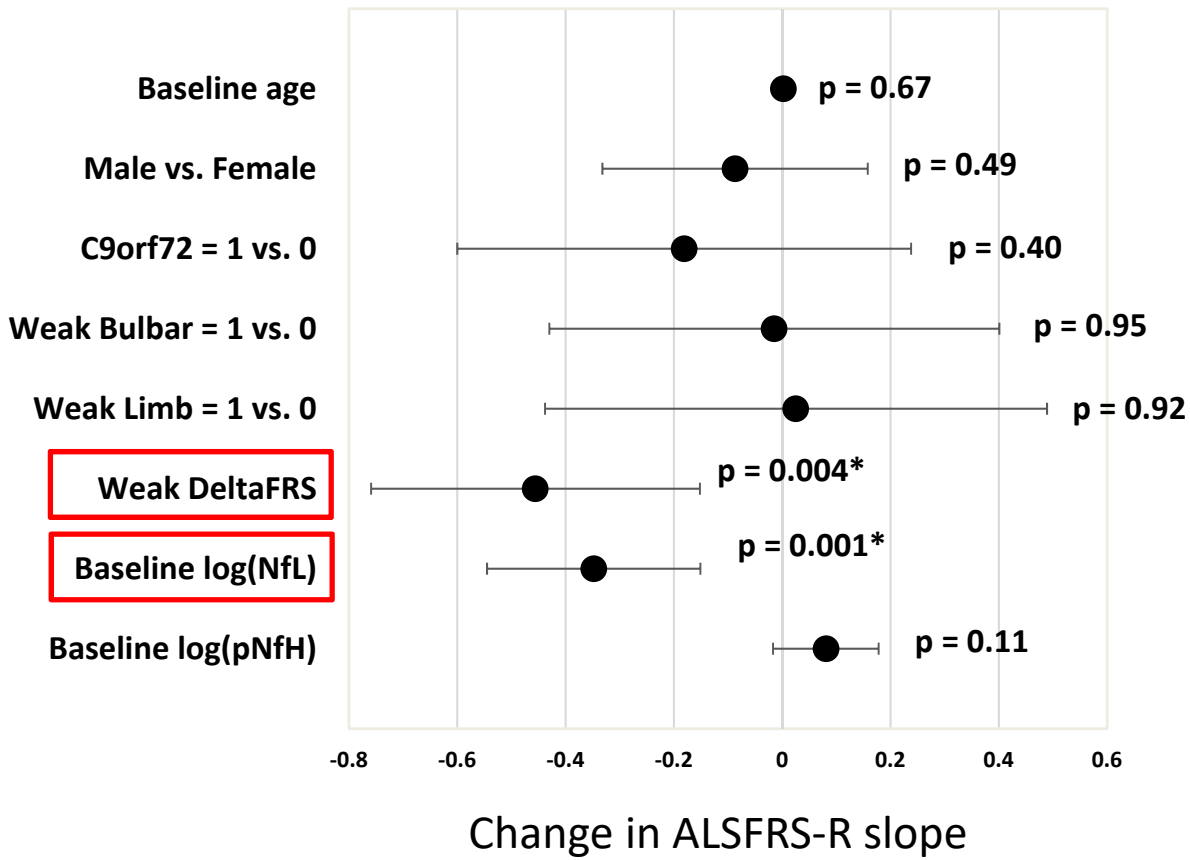
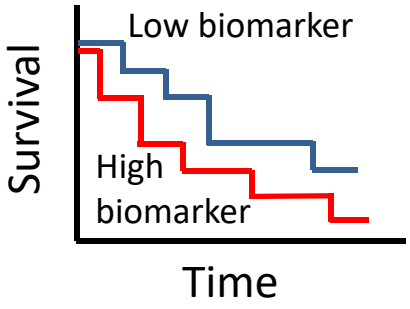
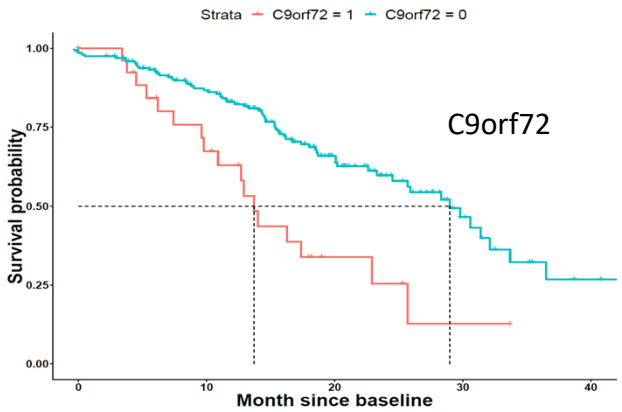
Prognostic Utility of Serum Neurofilament



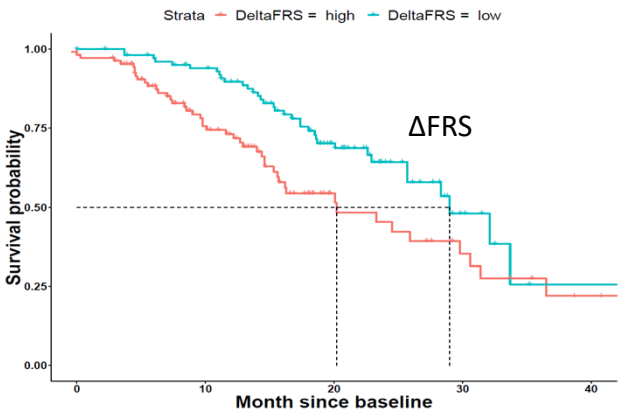


Prognostic Utility of Serum Neurofilament



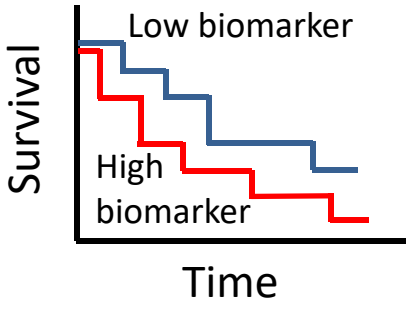


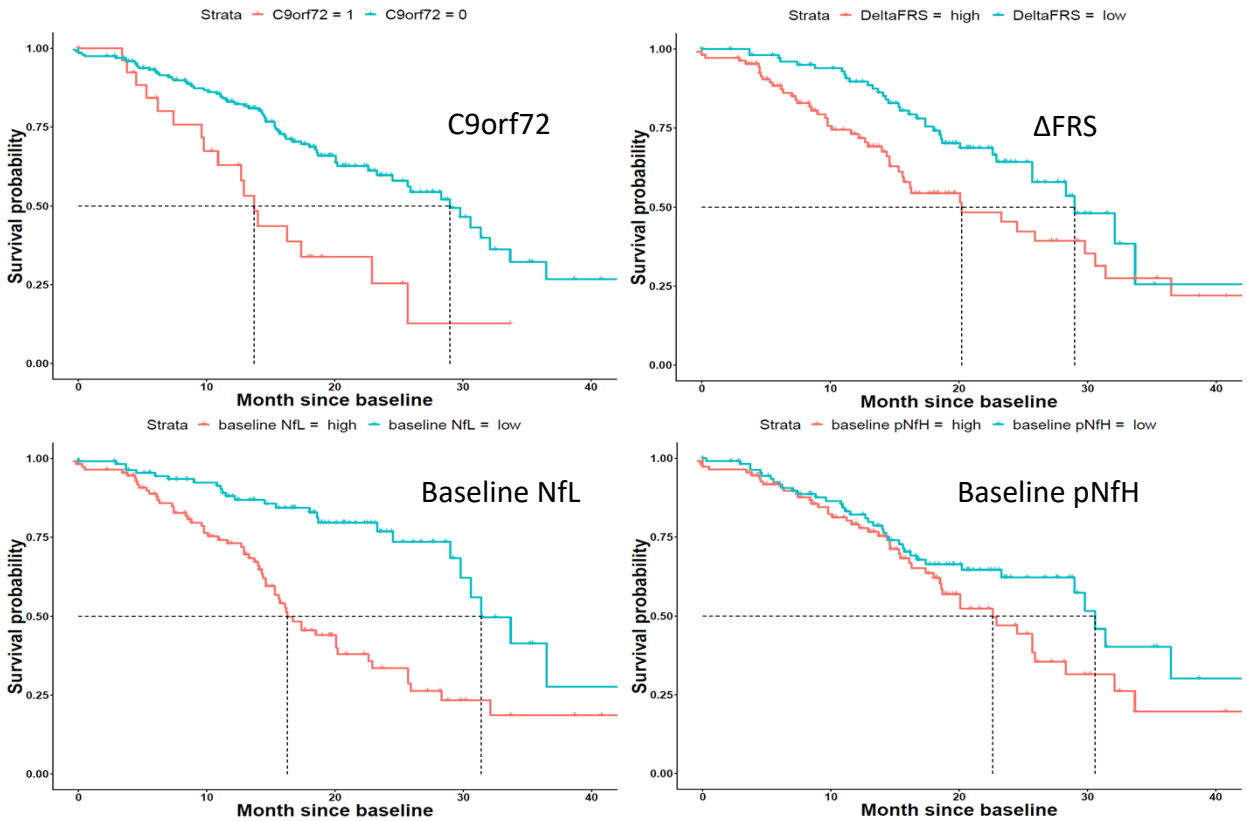
Baseline NfL



Baseline pNfH

Prognostic Utility of Serum Neurofilament





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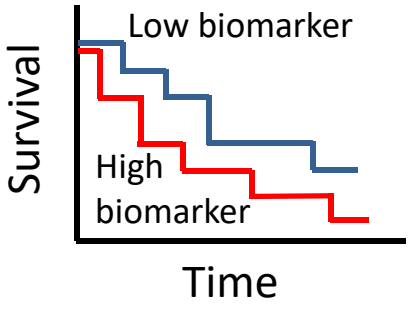

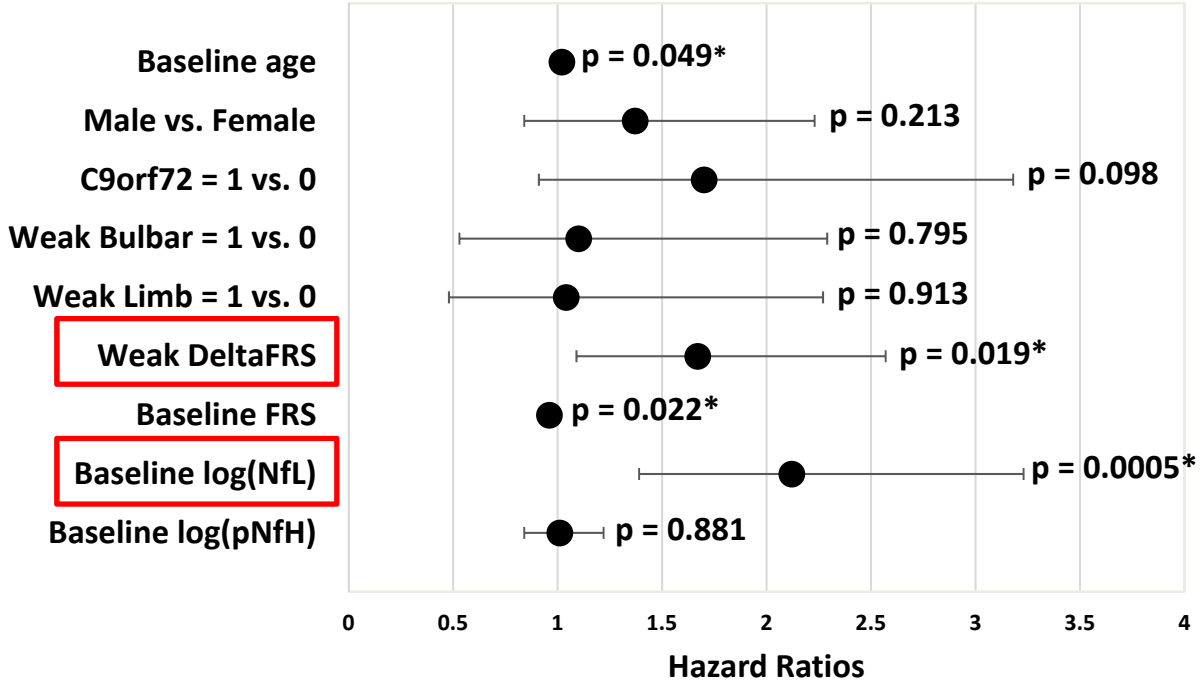

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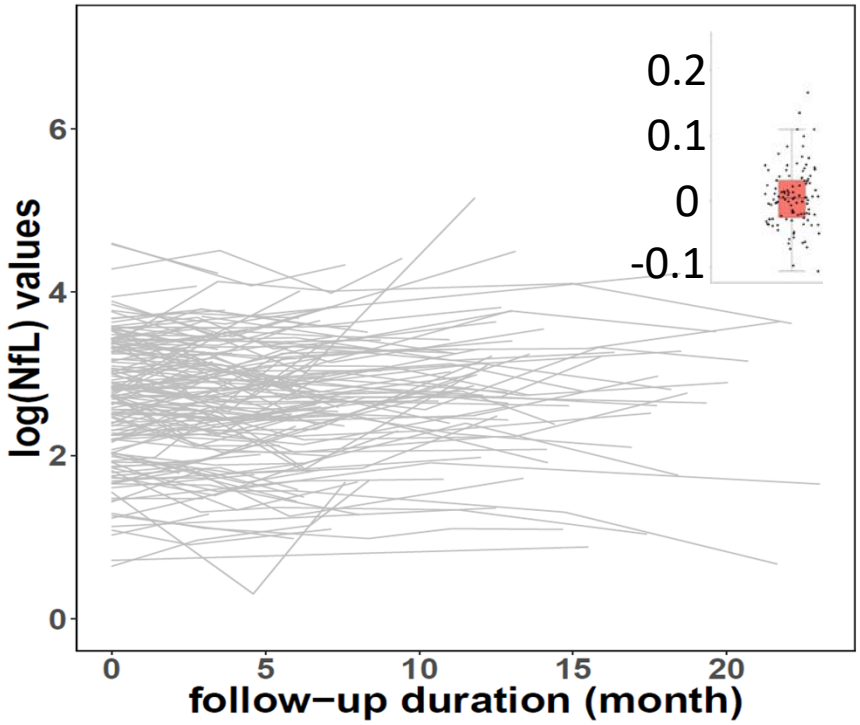
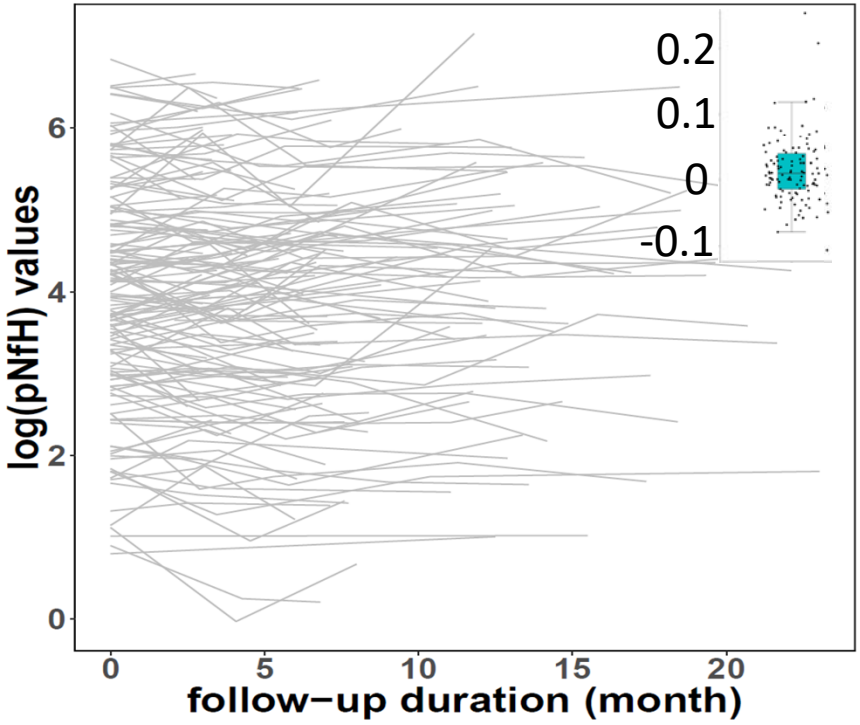
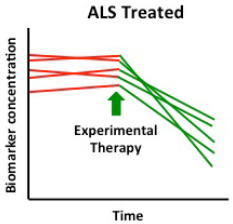
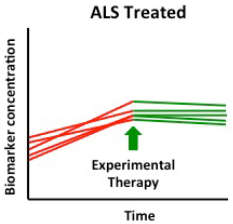
Potential Pharmacodynamic Utility of Neurofilaments

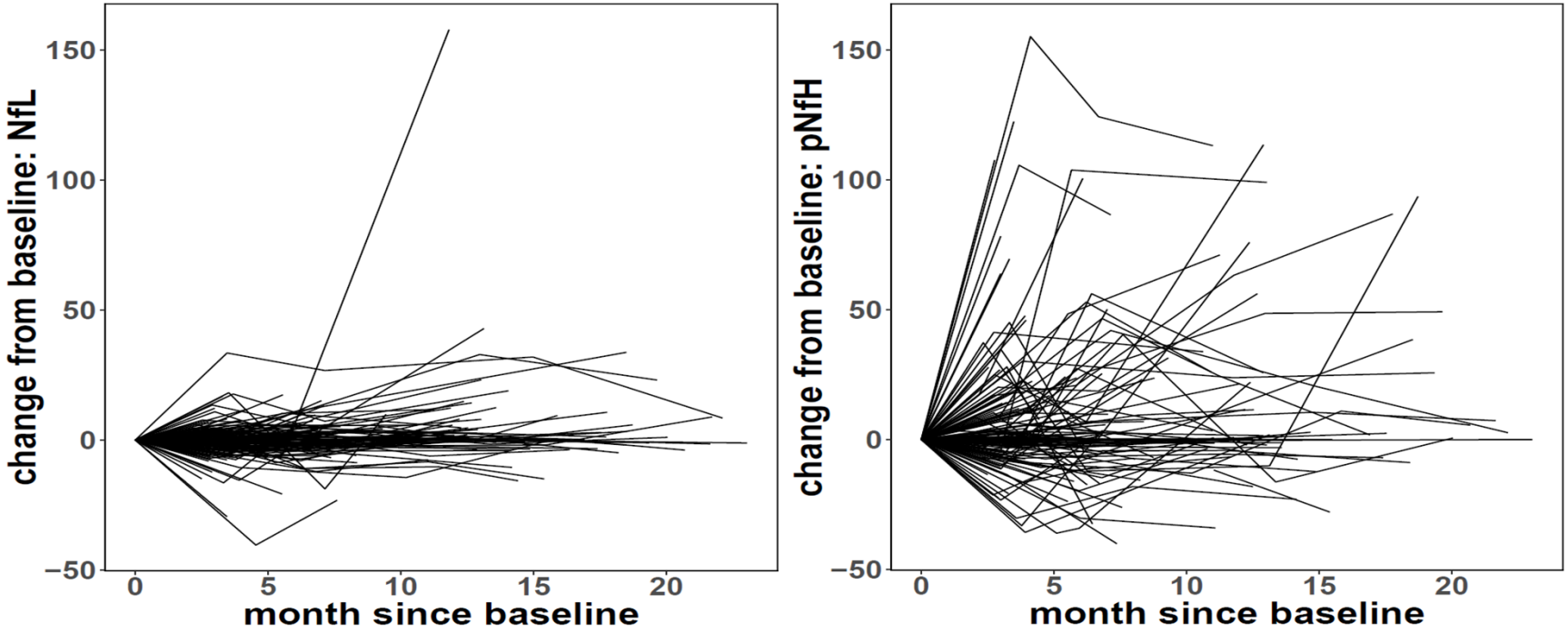








Potential Pharmacodynamic Utility of Neurofilaments



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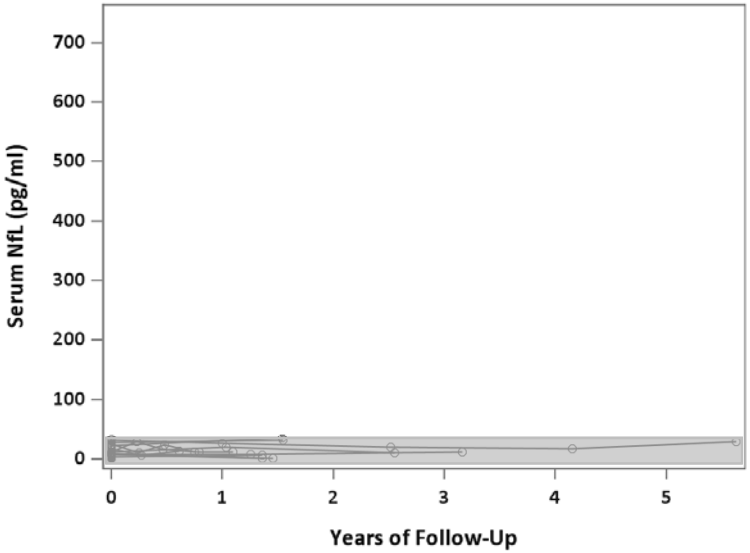
The *Pre-fALS* Study

- *Pre-Symptomatic Familial ALS*; initiated in 2007
- Longitudinal natural history and biomarker study of people at genetic risk for ALS
- Includes carriers of any ALS-causing gene mutation, the only population known to be *at risk* for ALS
  - *SOD1, C9orf72, TARDBP, FUS, VCP,* etc.
  - Option to learn result of genetic testing or not
- Goals
  - Identify biomarker of pre-symptomatic disease and/or predictors of symptomatic disease
  - Prepare for a disease prevention trial

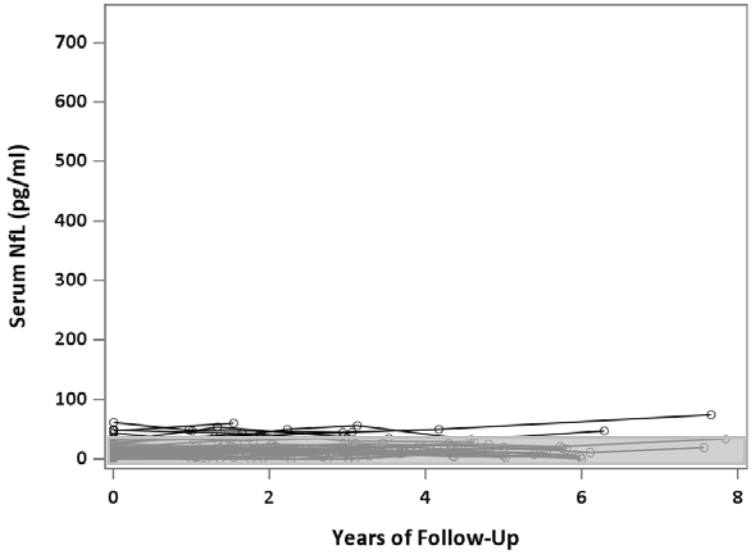
Benatar and Wuu. Neurology 2012, 79:1732-1739

Serum NfL: Longitudinal

Controls



At-risk



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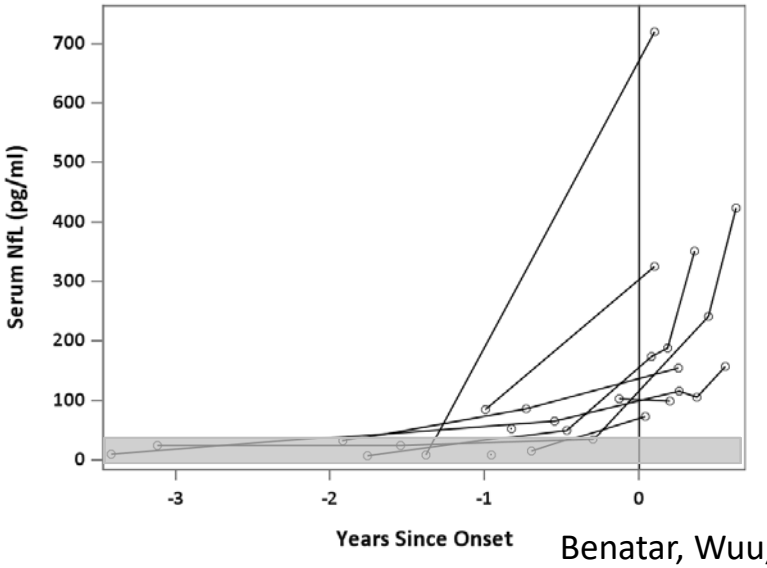
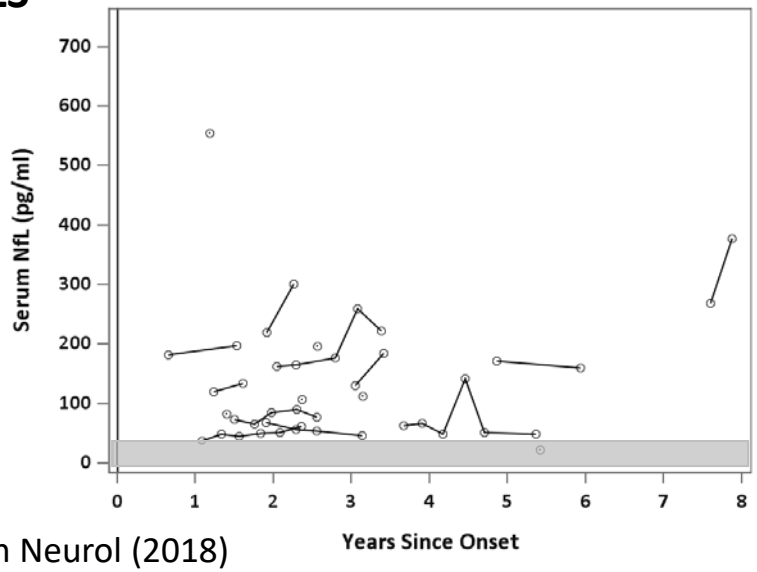
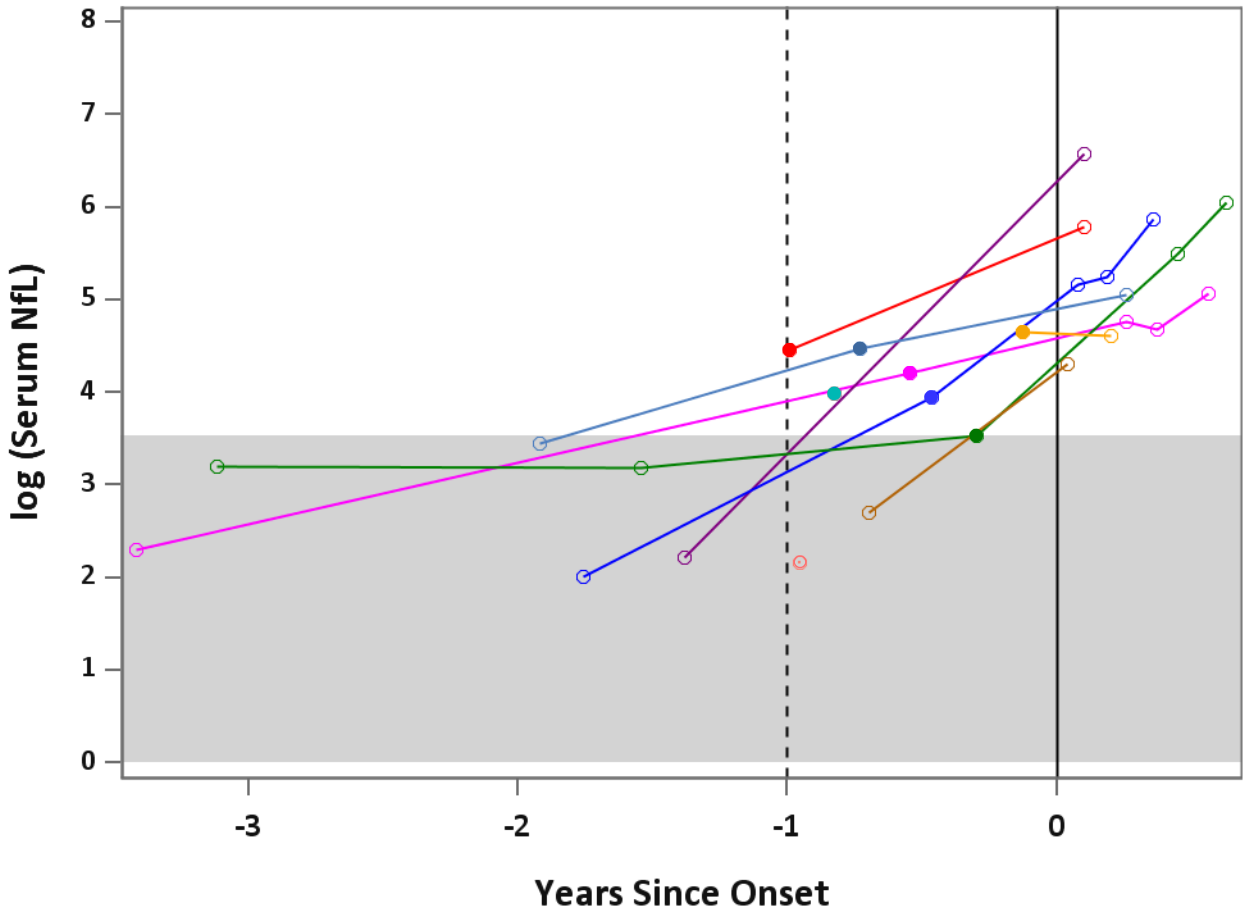


ALS



Benatar, Wuu, et al. Ann Neurol (2018)

Converter: Longitudinal Serum NfL



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Benatar, Wuu, et al. Ann Neurol (2018)

Conclusions

- Biomarkers have great potential to aid therapeutic development
- Critically important to:
  - Follow discovery with validation (analytic & clinical)
  - Develop with a view to a specific ‘context of use’

Discussion & Questions