The time taken by the ALSFRS-R to decrease to 50% (D50) in a sigmoidal decay model sufficiently describes the disease course of amyotrophic lateral sclerosis.
ΔFRS and Progression; how much can it really tell us?

\[
\Delta FRS = \frac{(48 - \text{ALSFRS-R score at diagnosis})}{\text{disease duration}}
\]

Kimura et al. 2006
1) **No established threshold** which represents important transitional point in functional status or progression type

**Neurofilament light chain**
A prognostic biomarker in amyotrophic lateral sclerosis

ΔFRS < 0.5 “Slow”
ΔFRS > 1 “Fast”

**Elevated cerebrospinal fluid neurofilament light levels in patients with amyotrophic lateral sclerosis: a possible marker of disease severity and progression**

ΔFRS < 0.71 “Slow”
ΔFRS > 0.71 “Fast”

**Phosphorylated neurofilament heavy subunit (pNF-H) in peripheral blood and CSF as a potential prognostic biomarker in amyotrophic lateral sclerosis**

ΔFRS < 0.8 “Slow”
ΔFRS > 0.8 “Fast”

**Immune reactivity to neurofilament proteins in the clinical staging of amyotrophic lateral sclerosis**

ΔFRS < 0.46 “Slow”
ΔFRS > 1.2 “Fast”
2) Presumes linearity
3) Reflects progression at **circumscribed time point**
Capture and Describe Disease Course

- Derived from regularly collected ALSFRS-R scores
- **D50**: Time taken for ALSFRS-R to fall by 50%
- **dx**: Slope of decrease

**D50**

- Full Health
- Maximum Disease

**Disease Duration [months]**

**ALSFRS-R score**
Chart Generator
© Julian Grosskreutz 2016

Howto:
1. Generate query from NMA database
2. Filter this query to Your needs (< 84000 entries)
3. Copy the query into the worksheet source
4. Click "Get source info" to populate headers
5. Adjust sort and filter settings to Your needs
6. Select configuration of charts
7. Click "Generate Diagram" optionally enable "Run fit"
8. Be happy.

If You change the settings of Your charts, remember You can save the style as custom style!

Sort Raw Data by
1. pars codename
2. offset diag frs
3. offset diag frs

Filter Raw Data per Unique value
1. offset_diag_frs
2. offset_diag_frs
3. offset_diag_frs

Chart 1
X-Axis: offset diag frs
Y-Axis 1: frs tot
Y-Axis 2:

Impose Limits on dataset
Min Number of ALFRS-R: 1, ok
Max Number included: 100, ok
Threshold ALSFRS-R: 48, ok
How does ALSFRS-R frequency affect model robustness?
Real patient data: “fast”, “intermediate” and “slow” progressors
- Normalize absolute months elapsed in disease course by individual D50 values
Potential for Phase Classification
D50 and Contemporary Staging Systems

Milestone Timing = Time taken to reach stage from onset/disease duration
0 = symptom onset
1 = death
Key Takeaways

- Strong linear correlation between D50 and dx: D50 can act as stand-alone parameter
- Sampling at any time point can be viewed in context of D50
- Accessible and descriptive indice
- Strong correlation with “hard” survival endpoint
- Collinearity with contemporary functional (MITOS) and clinical (King staging systems
Utility and Implementation

- Map and describe **disease course**
- Provides value over & above FRS scores for **disease progression**
- Increased **analytical utility**
- **Biomarker development** and testing
- Understand **disease mechanisms** in different phases

\[ R = 0.340 \]
\[ p = 0.002 \]
Open Questions and Further Directions

- Cohort expansion and replication
- Establishing mathematical cutoffs for fast vs. slow
- Investigate utility in clinical trial populations vs. general ALS populations
- Further probe relation to other staging systems
- Apply to stratification by site of onset, phenotype etc.
- Test relation to other clinical factors (muscle strength, QOL, cognitive decline)

(Also taking submissions for an alternative naming system!)
Acknowledgements
Methodology Overview

- $n = 393$
- Dynamic presets derived using conventional $\Delta$FRS
- $n = 352$
- Microsoft Excel Add-In Solver Tool
- $D_{50}$
- $dx$

$$y = \frac{48}{1 + e^{\frac{(x-D_{50})}{dx}}}$$
Fast Progressors

D50

MITOS

KING’s

X AXIS: STAGE/PAGE
Y AXIS: MILESTONE TIMING
Intermediate Progressors

**D50**

**MITOS**

**KING’s**

**X AXIS:** STAGE/PHASE

**Y AXIS:** MILESTONE TIMING
D50 Phasing and other Contemporary Staging Protocols

Milestone Timing = Time taken to reach stage from onset/disease duration

0 = symptom onset
1 = death

Mean Milestone Timings for Different Staging Systems:
- Fast Progressors (n = 10)
- Intermediate Progressors (n = 10)
- Full Cohort (n = 20)
References

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4456658/


http://jnnp.bmj.com/content/84/4/467.long

http://jnnp.bmj.com/content/85/3/274.long


KINGs

MITOS