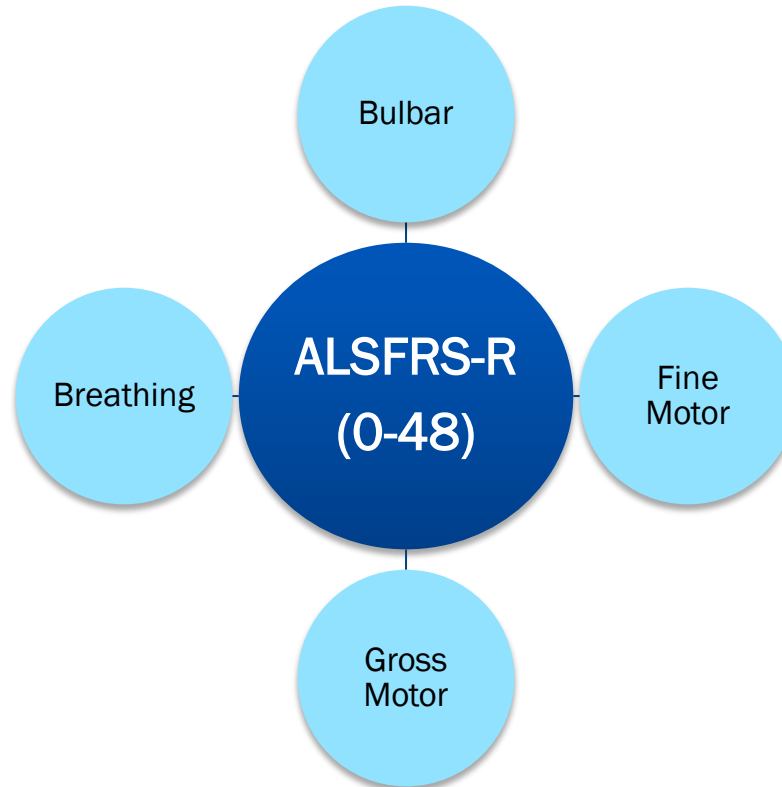


The time taken by the ALSFRS-R to decrease to 50% (D50) in a sigmoidal decay model sufficiently describes the disease course of amyotrophic lateral sclerosis

Nayana Gaur, Beatrice Stubendorff, Annekathrin Rodiger, Anne Gunkel, Monique Radscheidt, Tino Prell, Otto W. Witte, Julian Grosskreutz
Dept of Neurology, Jena University Hospital, Jena, Germany

European Network to Cure ALS 2017
Ljubljana, Slovenia

Δ FRS and Progression; how much can it really tell us?



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

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

$\Delta\text{FRS} < 0.5$ "Slow"

$\Delta\text{FRS} > 1$ "Fast"

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

$\Delta\text{FRS} < 0.71$ "Slow"

$\Delta\text{FRS} > 0.71$ "Fast"

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

$\Delta\text{FRS} < 0.8$ "Slow"

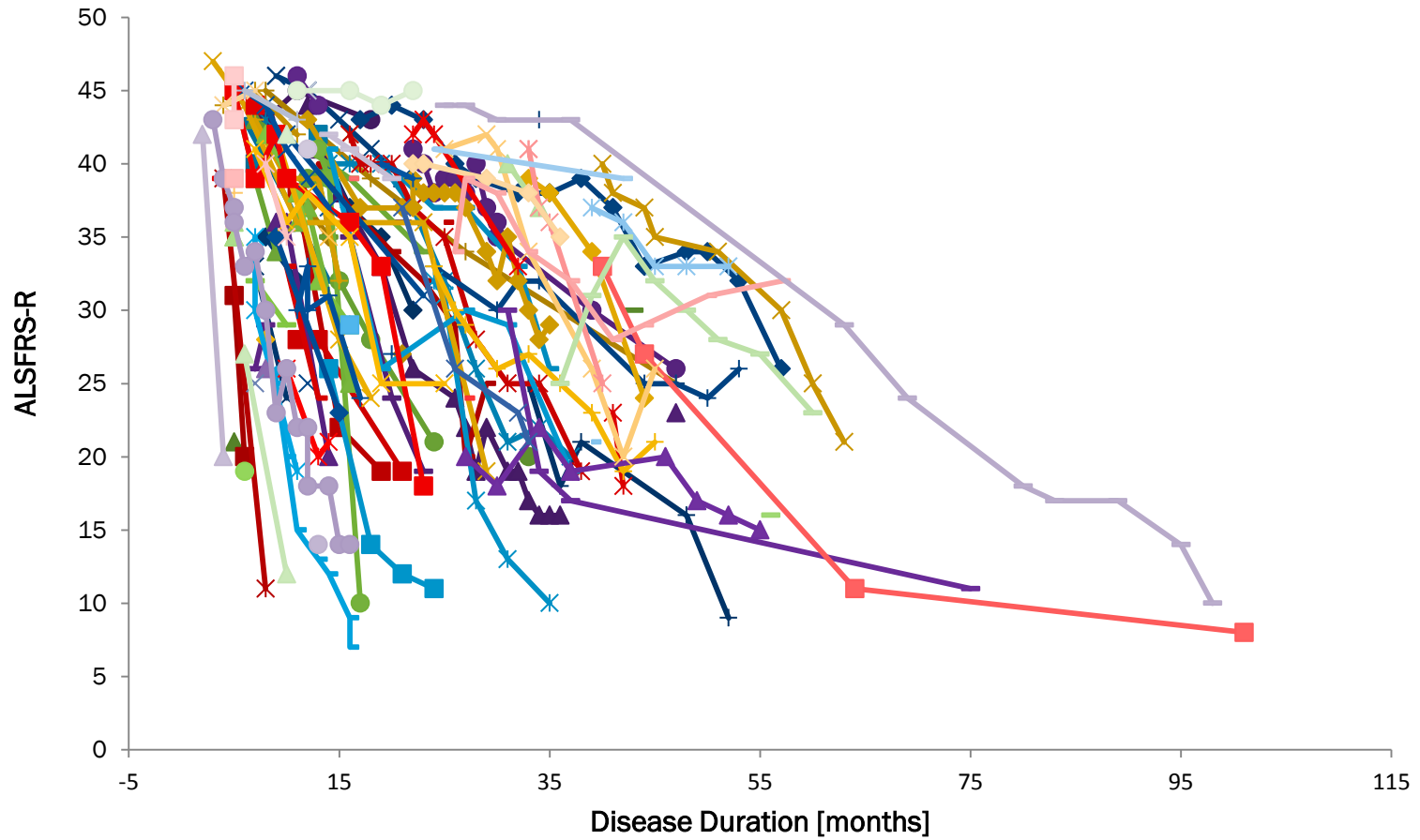
$\Delta\text{FRS} > 0.8$ "Fast"

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

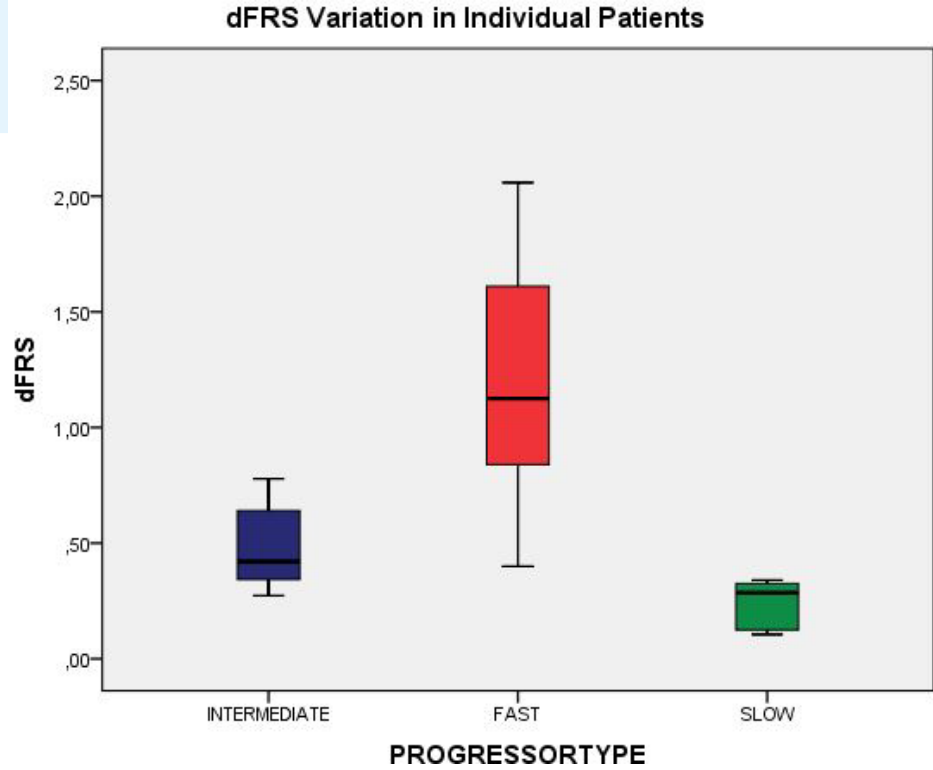
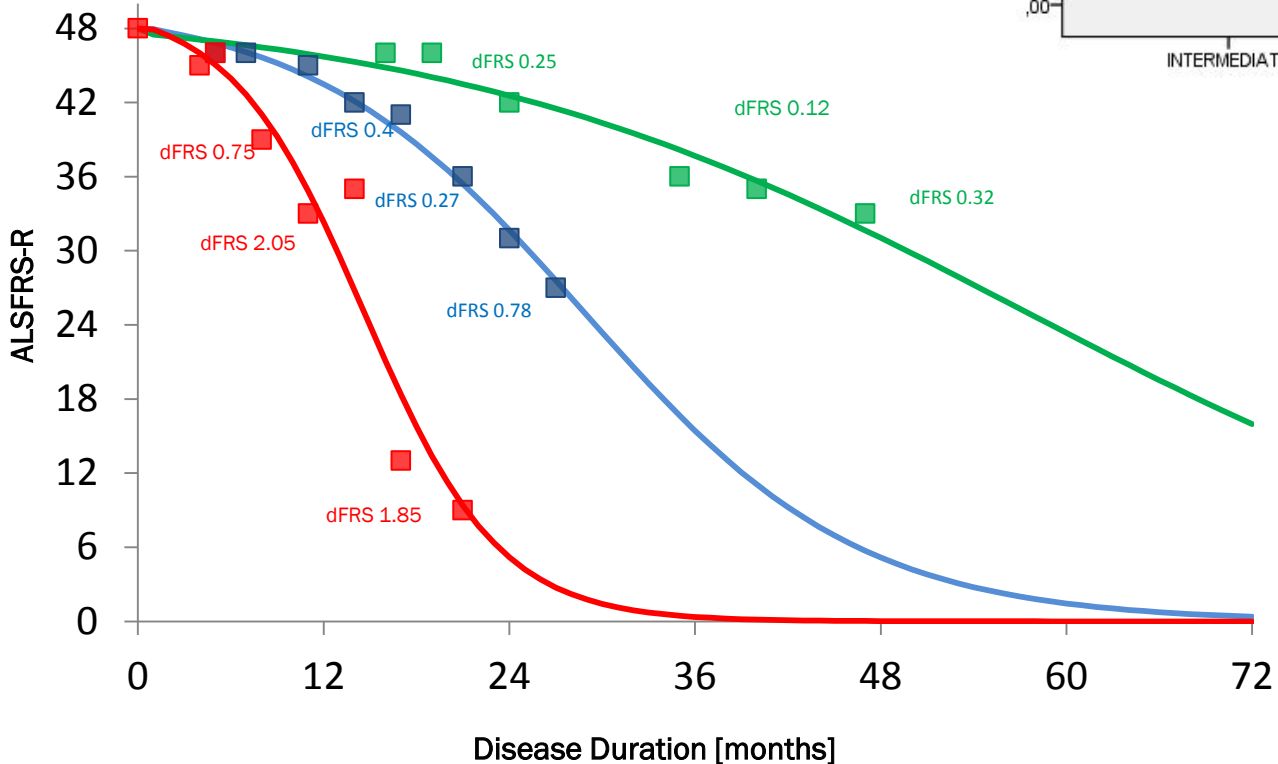
$\Delta\text{FRS} < 0.46$ "Slow"

$\Delta\text{FRS} > 1.2$ "Fast"

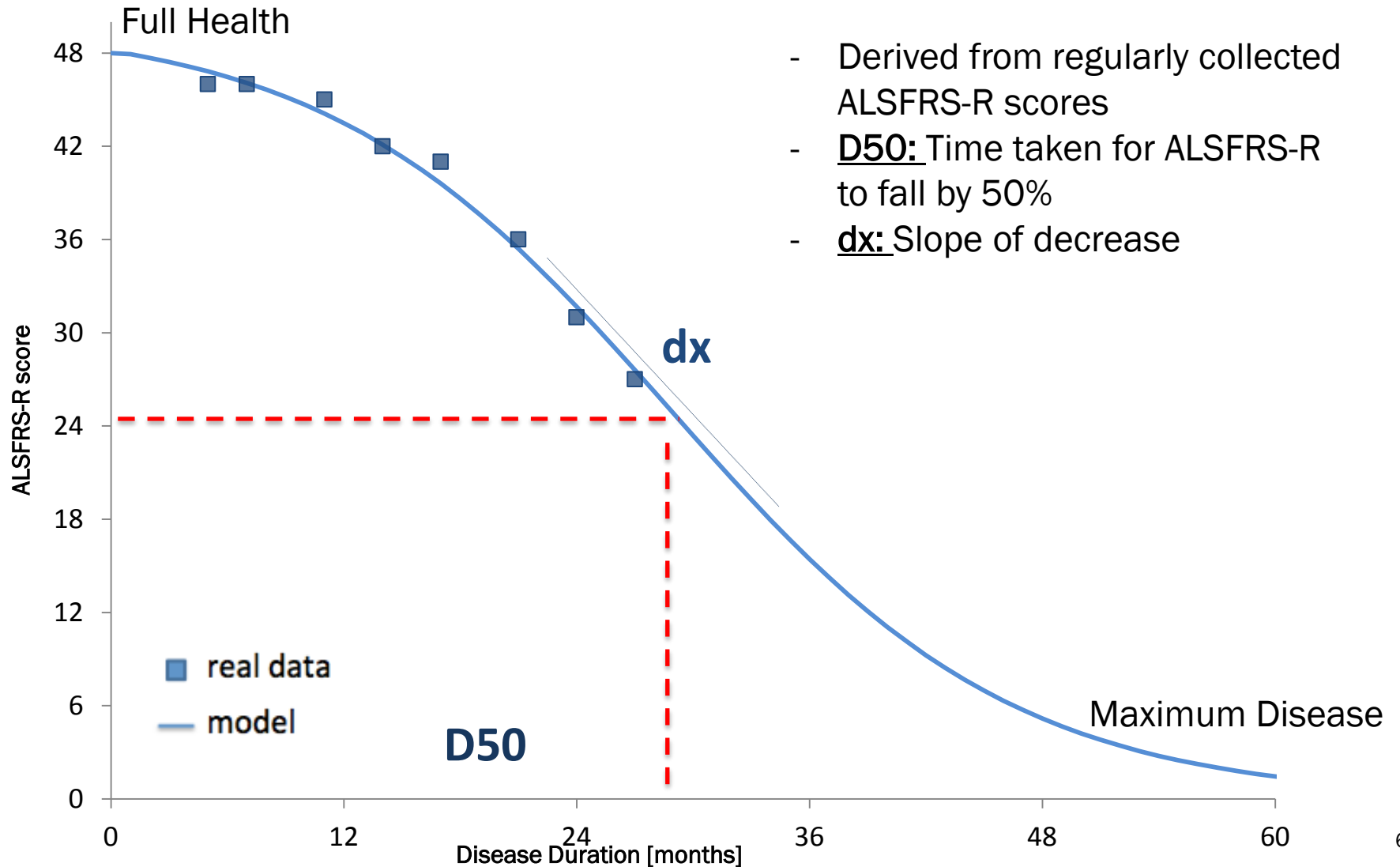
2) Presumes linearity



3) Reflects progression at circumscribed time point



Capture and Describe Disease Course



20161207_JENALS_Simulator.xlsm [Repariert] - Microsoft Excel

Chart Generator
© Julian Grosskreutz 2016

Get Source Info

Run Fit

Generate Diagram

Sort Row Data by

1. pers codename
2. offset diag frs
3. offset diag frs

Filter Raw Data per Unique value

offset_diag_frs

Howto

1. Generate query from NMA database
2. Filter this query to Your needs (< 64000 entries)
3. Copy the query into the worksheet source
4. Klick "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 !

Chart 1

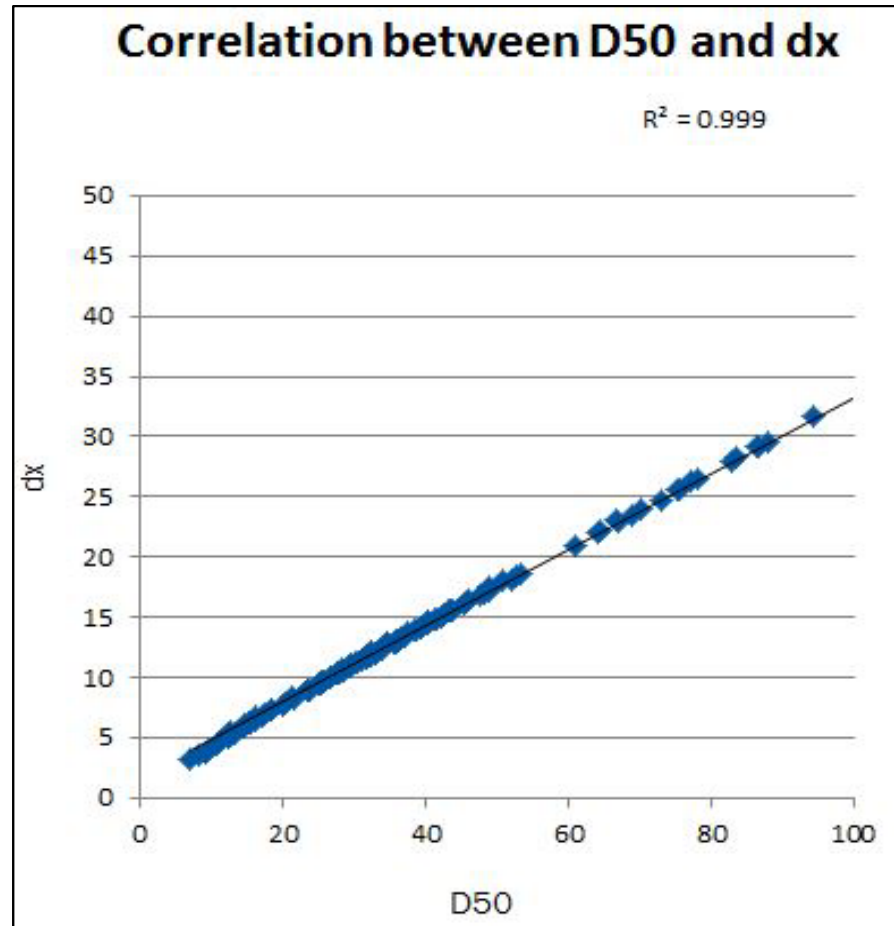
X-Axis: offset diag frs
Y-Axis 1: frs tot
Y-Axis 2:

Impose Limits on dataset

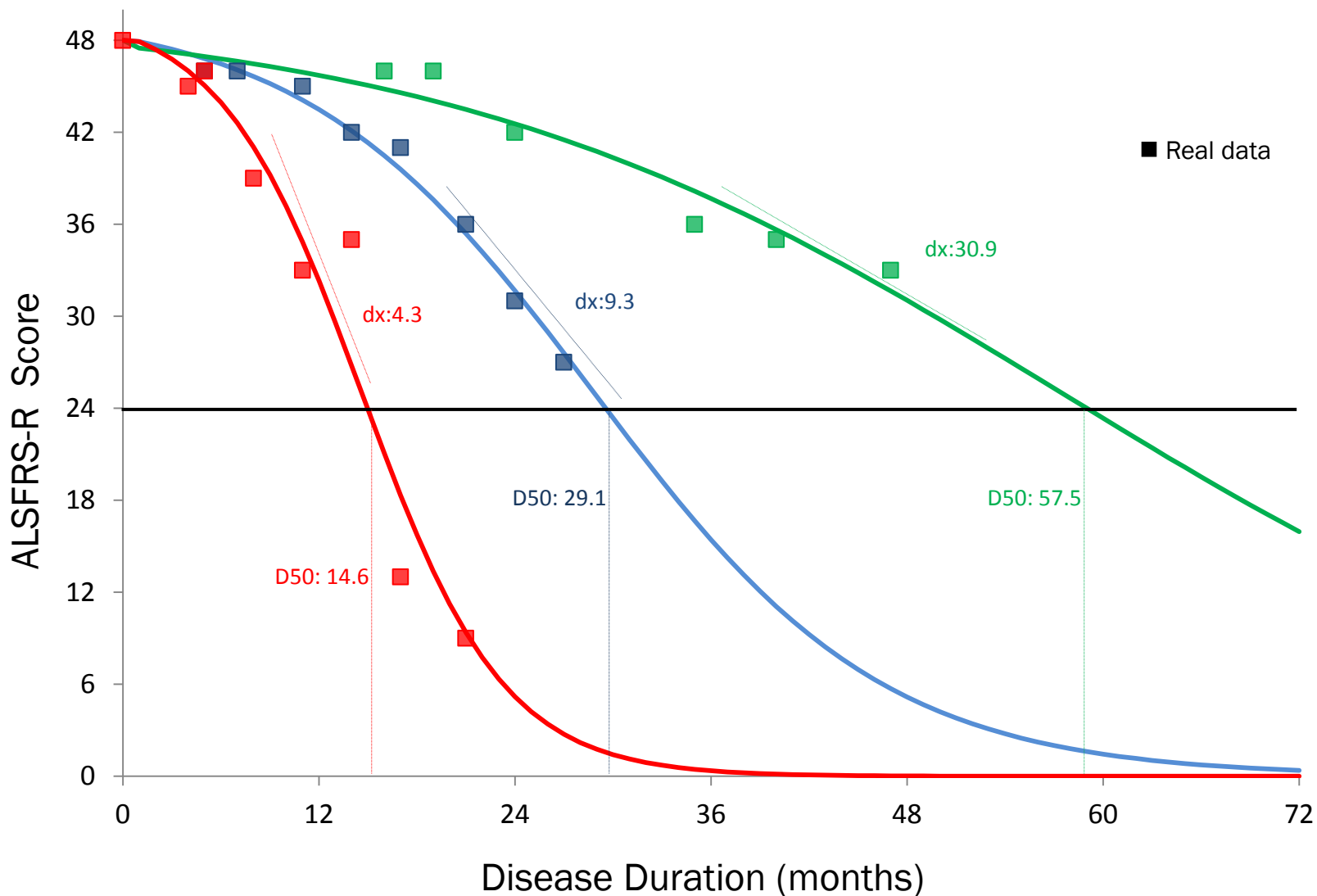
| | | |
|-----------------------|-----|----|
| Min Number of ALFRS-R | 1 | ok |
| Max Number included | 100 | ok |
| Threshold ALSFRS-R | 48 | ok |

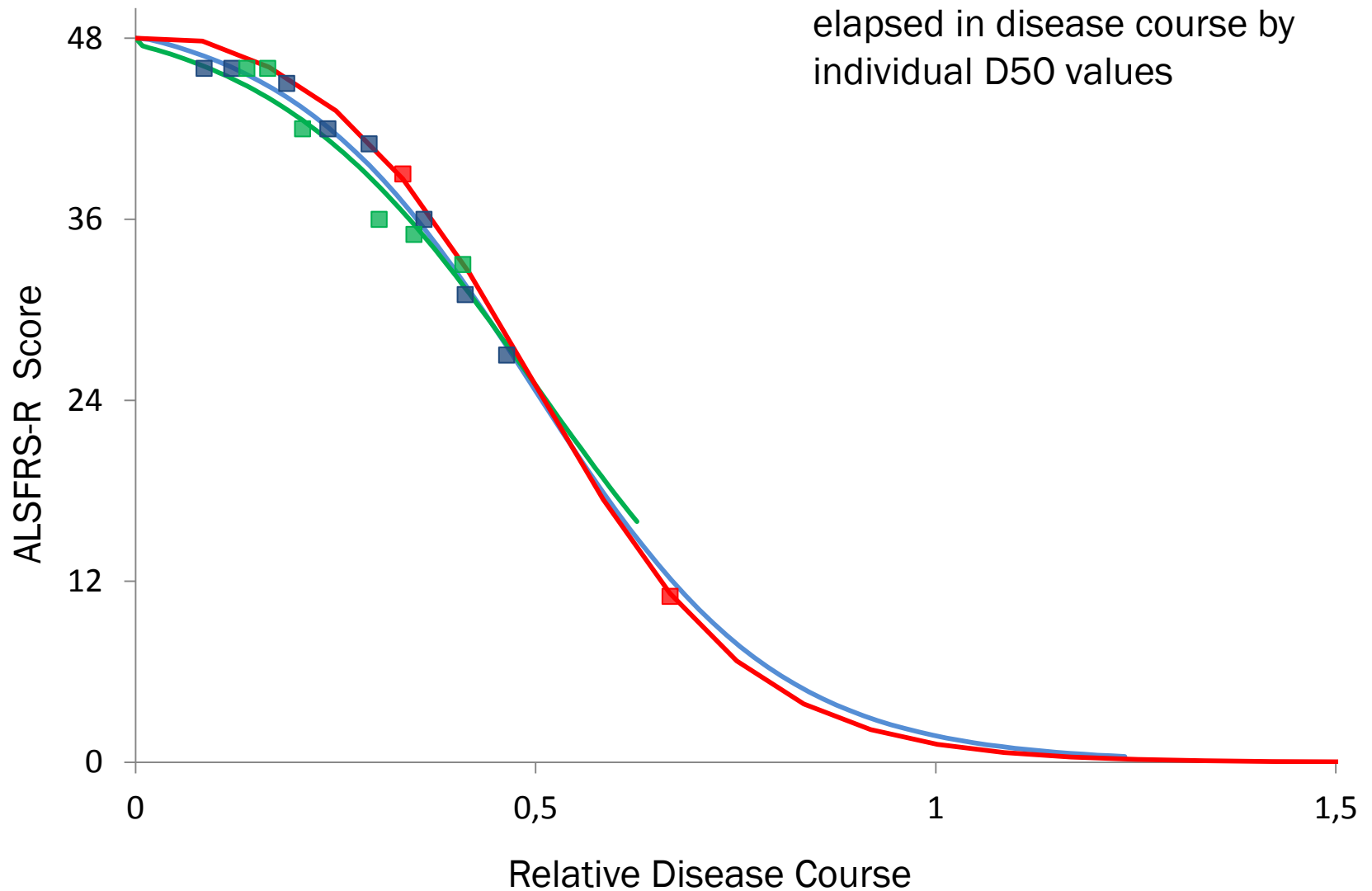
control source fit results ALSFRS-R_calc settings chart1 chart2 chart3 chart4 rawdata codes_OI addinfo rawdata_filtered

How does ALSFRS-R frequency affect model robustness?

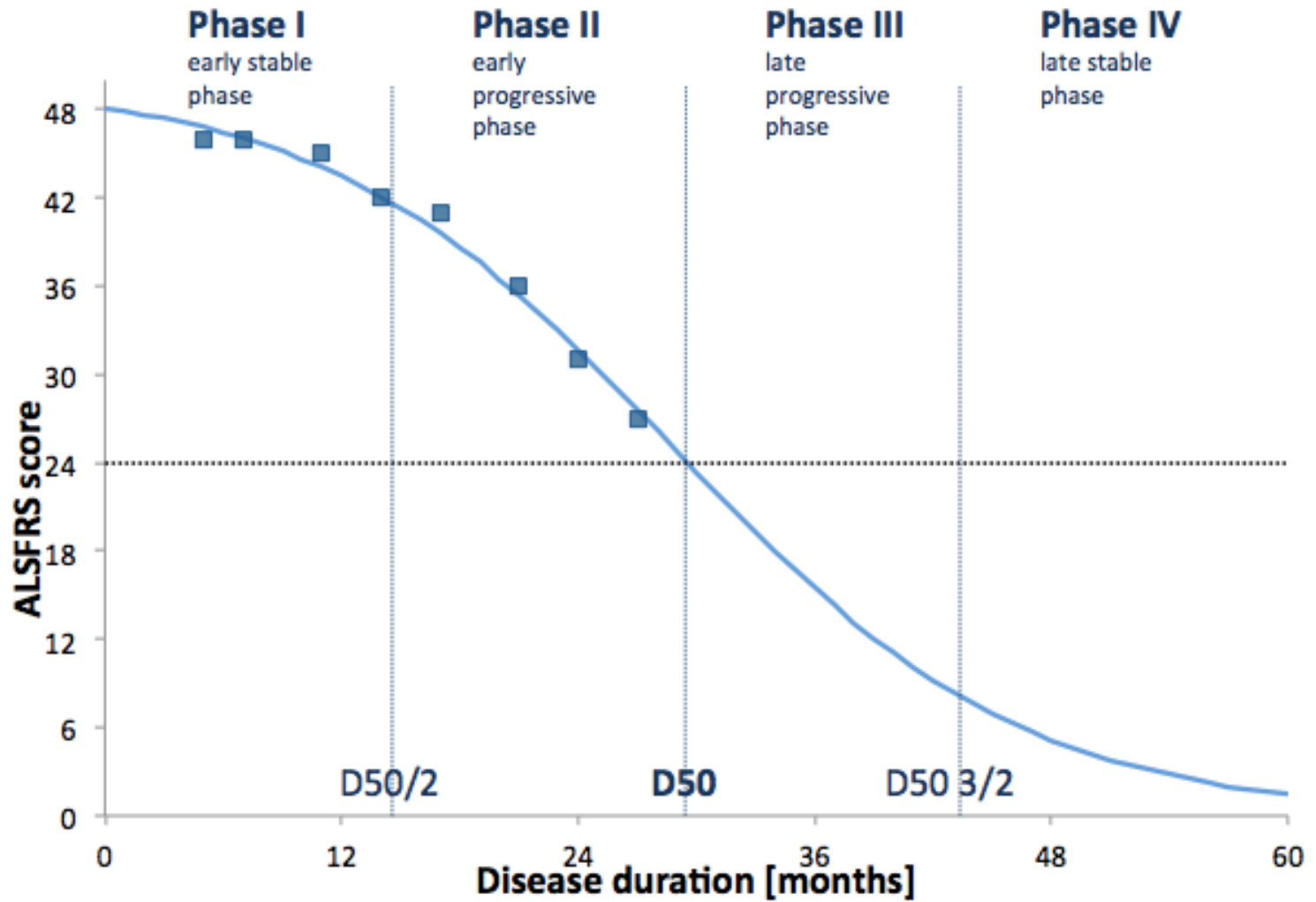


Real patient data: “fast”, “intermediate” and “slow” progressors





Potential for Phase Classification

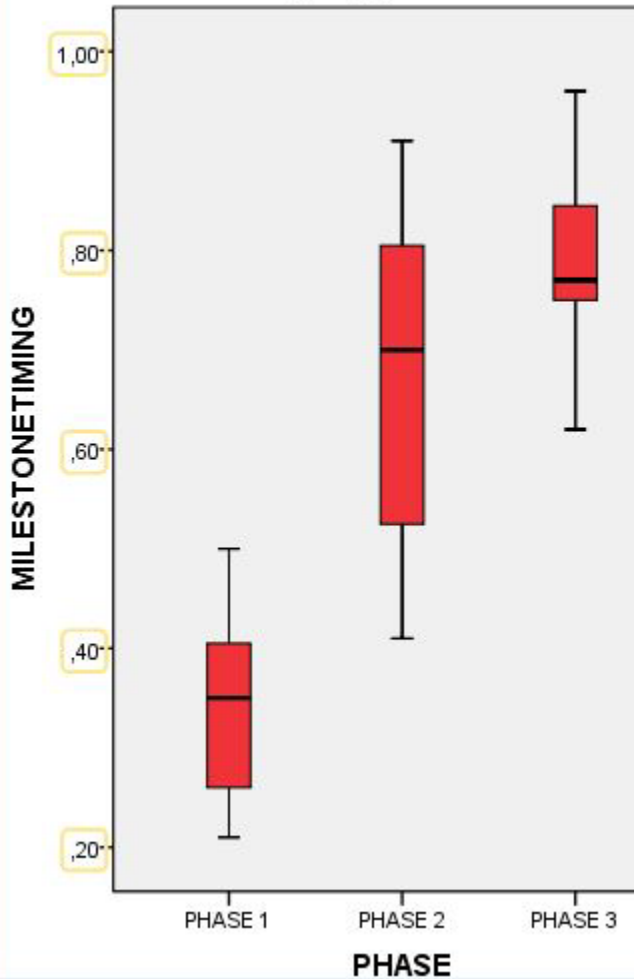


Milestone Timing = Time taken to reach stage from onset/disease duration

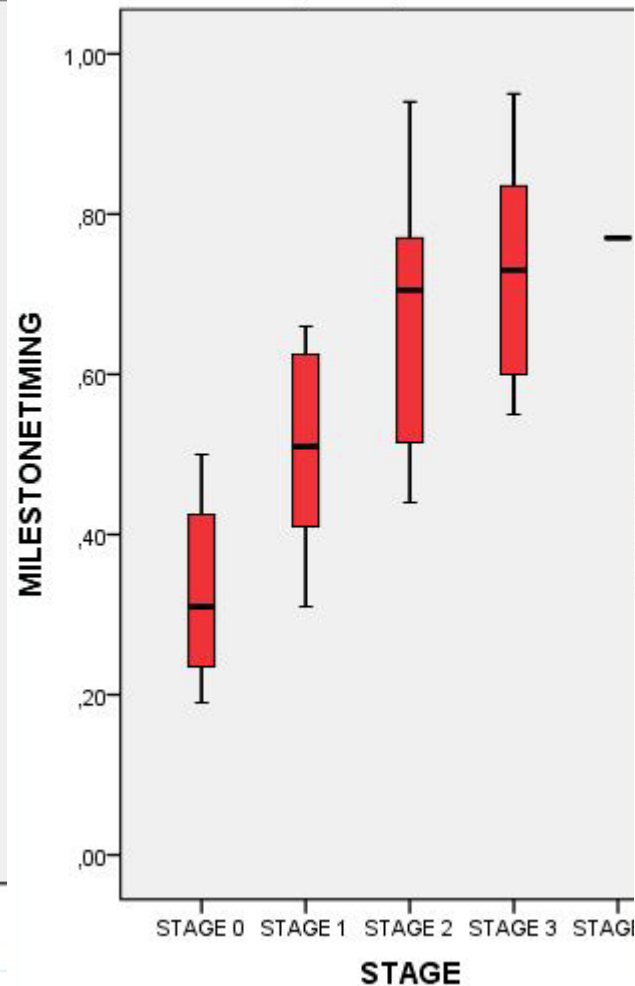
0 = symptom onset
1 = death

D50 and Contemporary Staging Systems

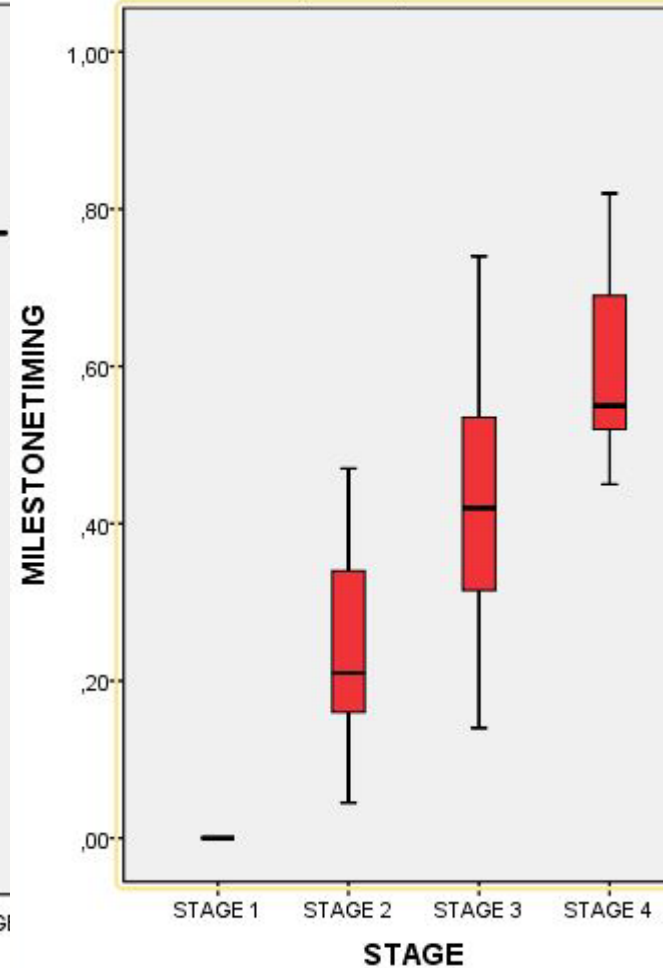
D50 JENA MILESTONE TIMINGS (n = 20)



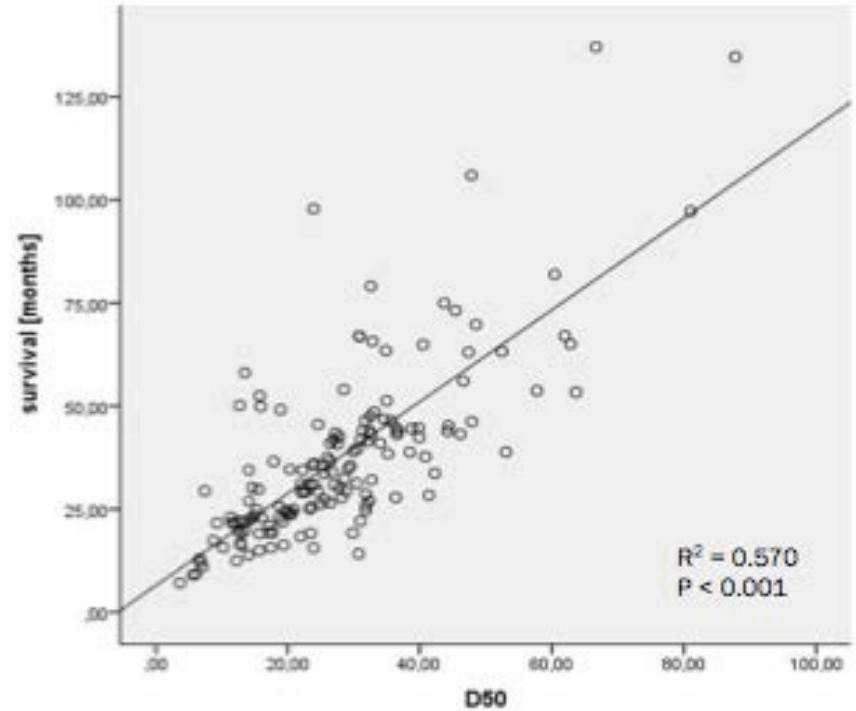
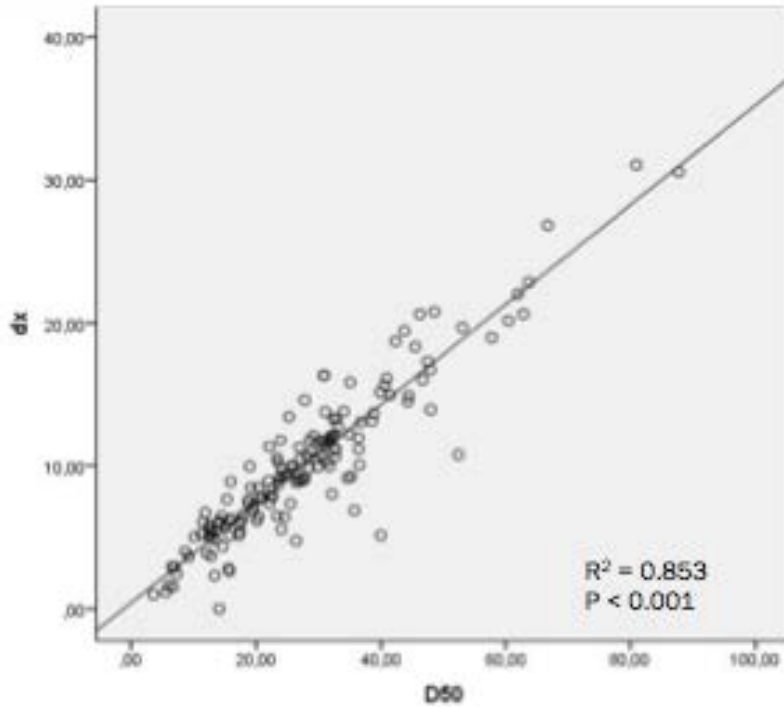
MITOS MILESTONE TIMINGS (n = 20)



KING'S MILESTONE TIMINGS (n = 20)



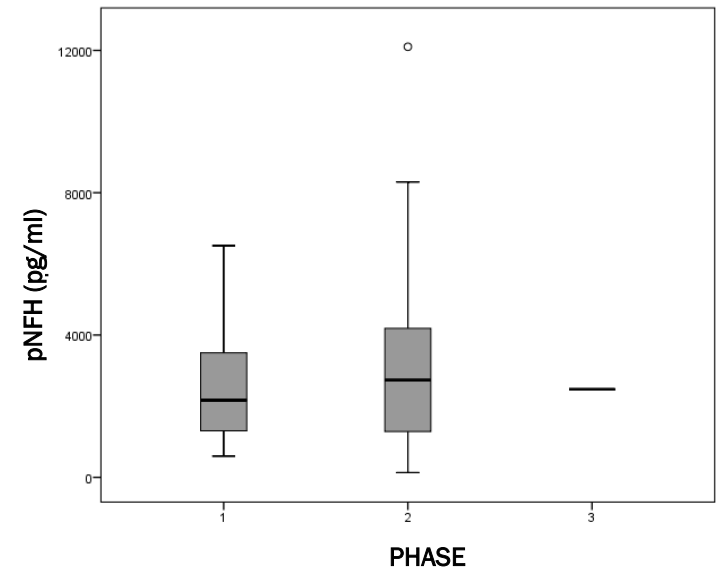
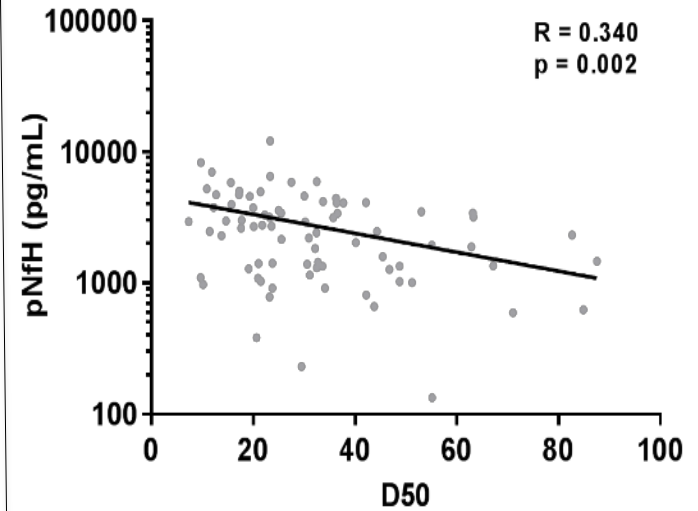
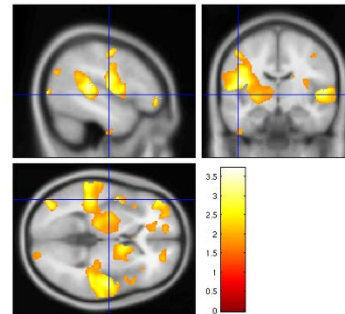
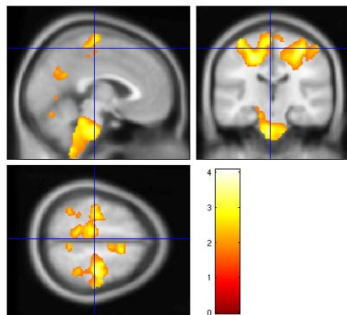
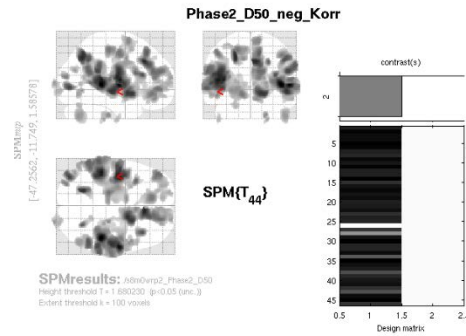
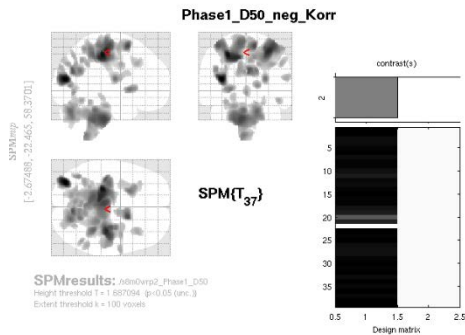
Key Takeaways



- 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

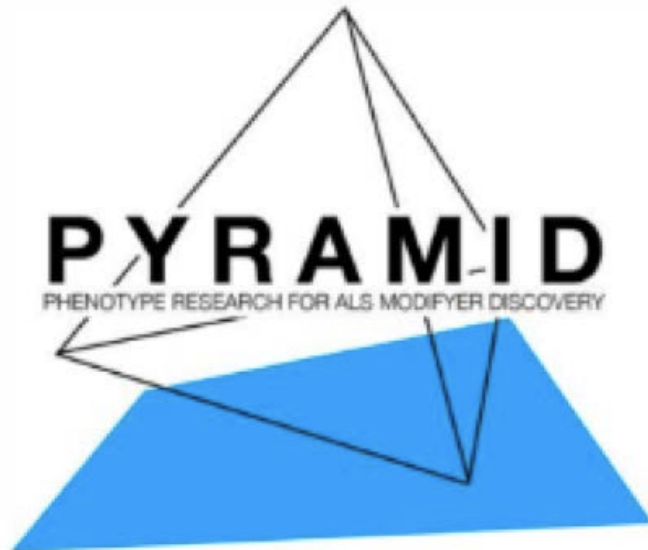


Open Questions and Further Directions

- 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)

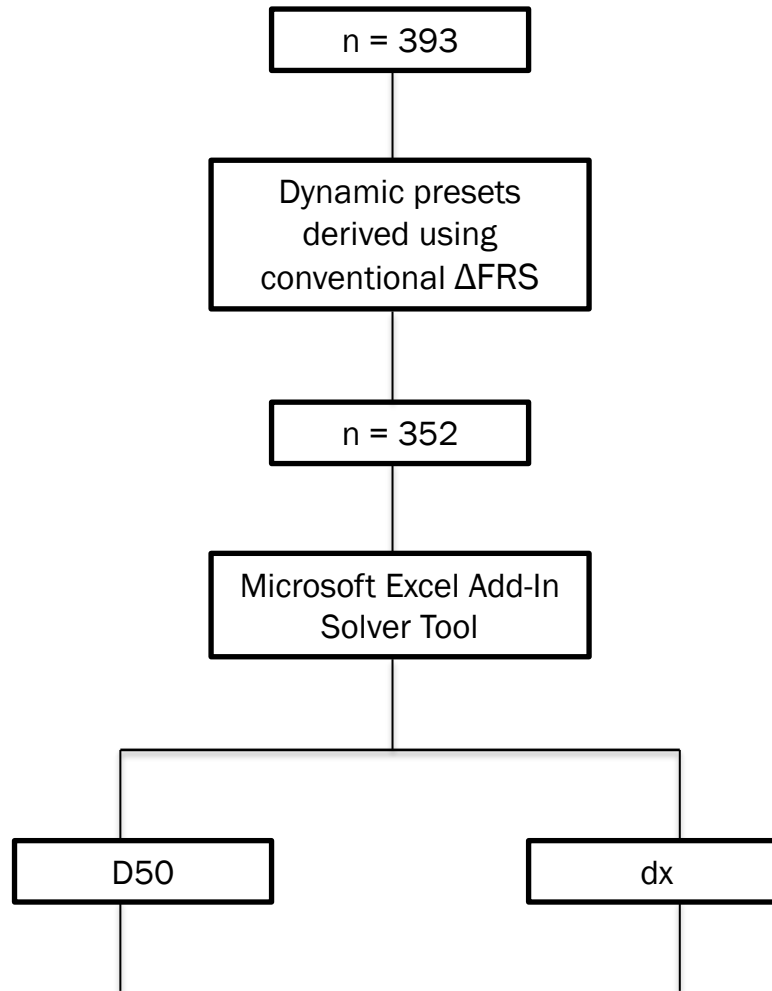
(Also taking submissions for an alternative naming system!)

Acknowledgements



Deutsche Gesellschaft für
Muskelkranke e.V. **DGM**

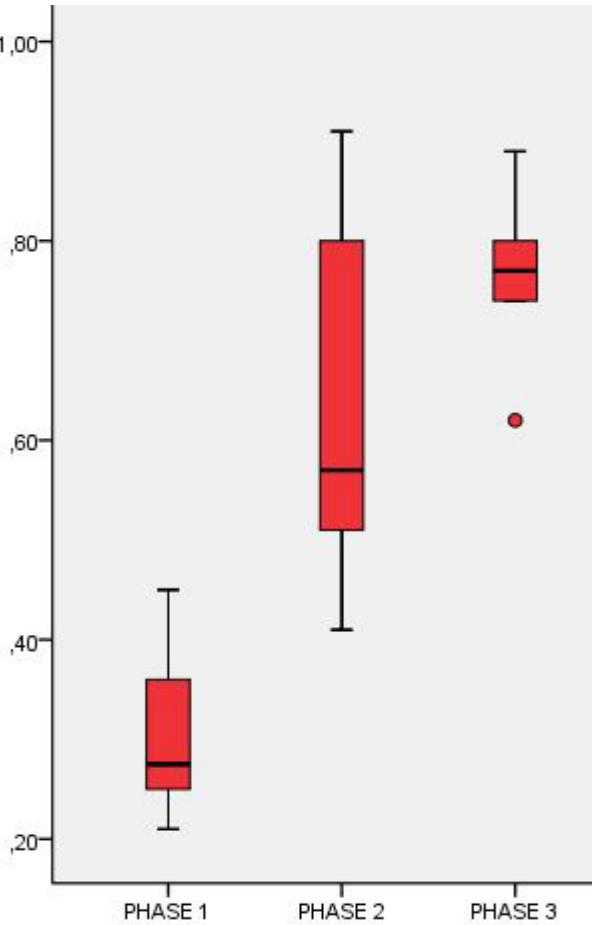
Methodology Overview



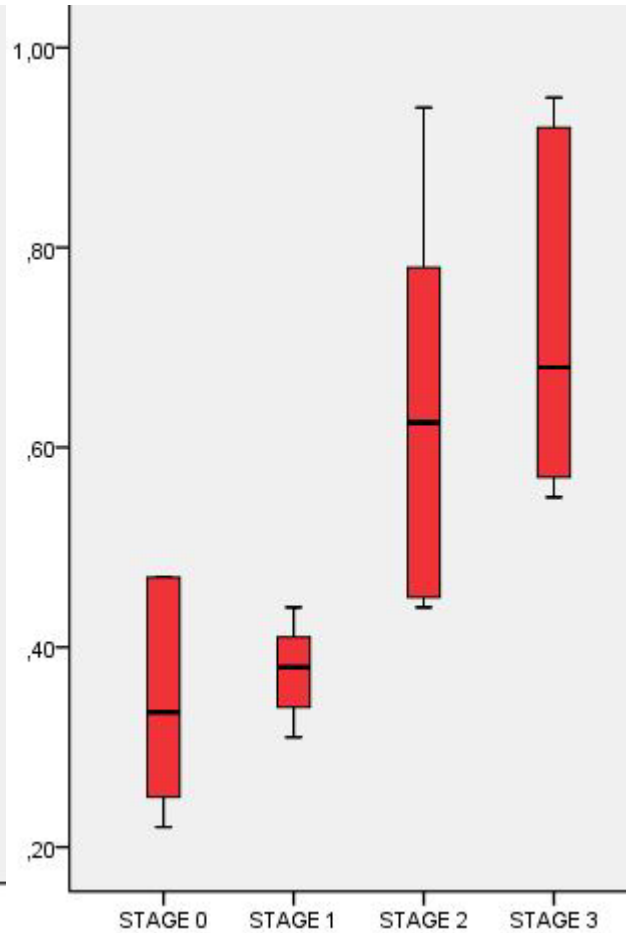
$$y = \frac{48}{1 + e^{\frac{(x-D50)}{dx}}}$$

Fast Progressors

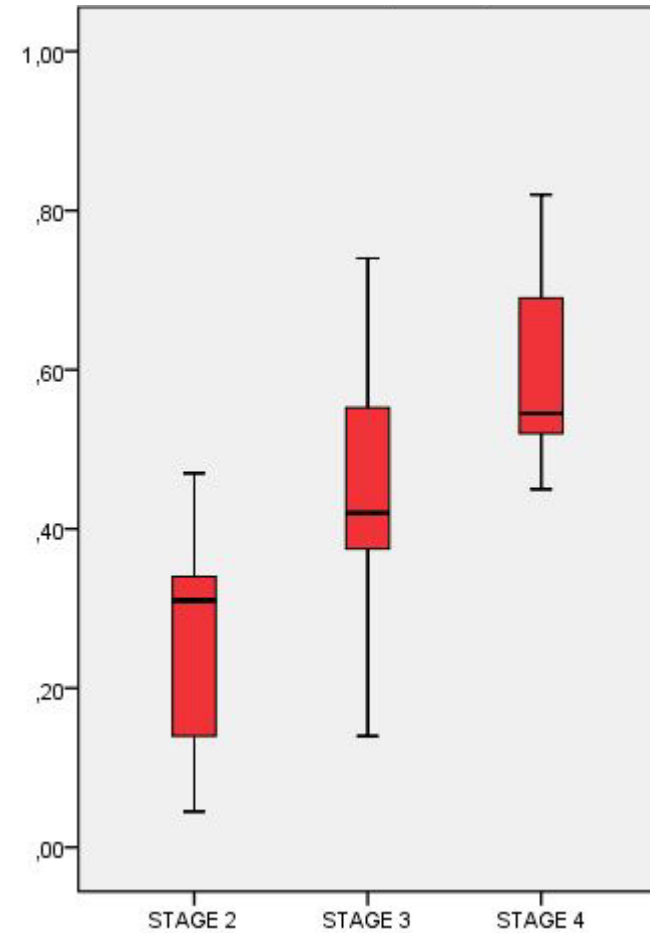
D50



MITOS



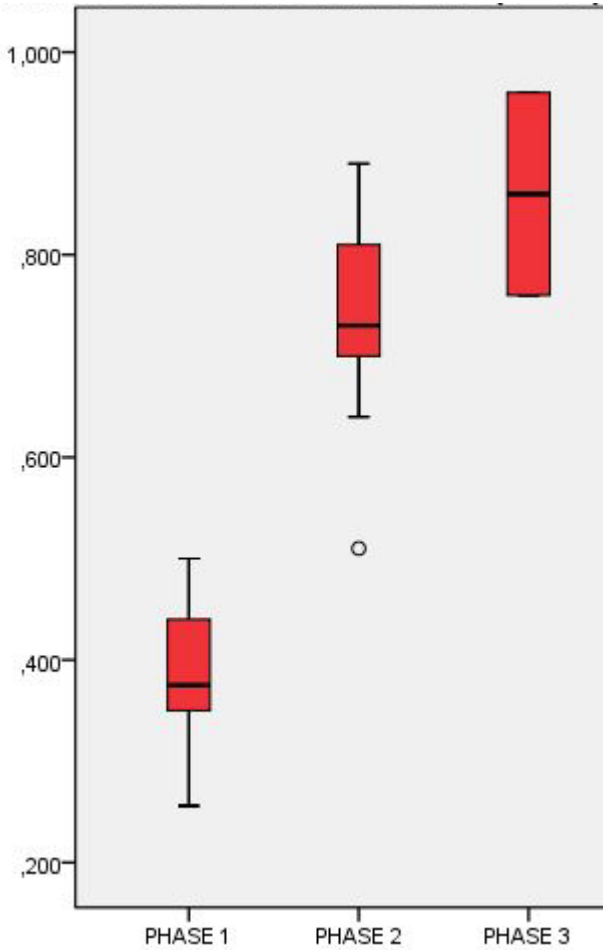
KING's



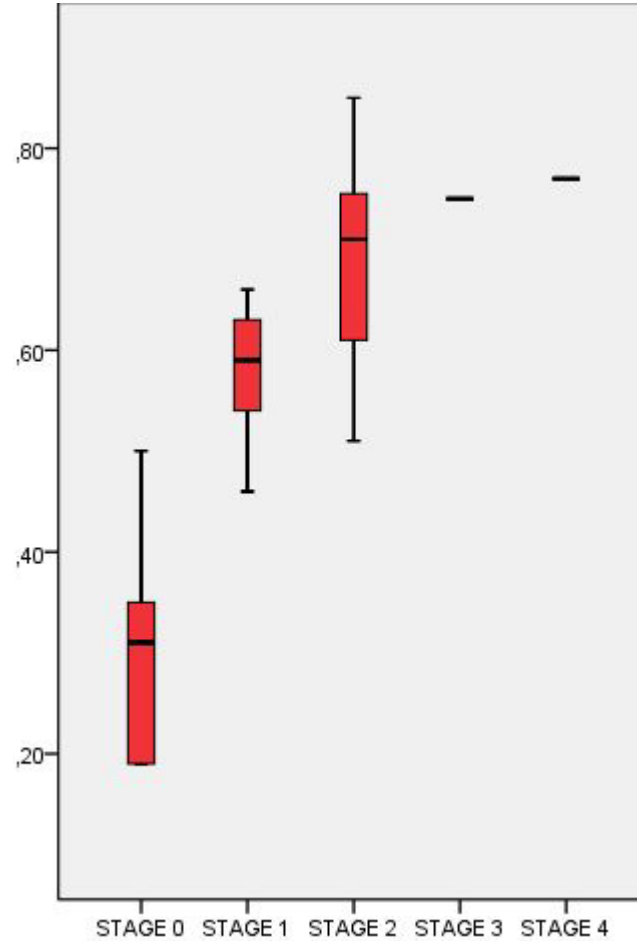
X AXIS: STAGE/PHASE
Y AXIS: MILESTONE TIMING

Intermediate Progressors

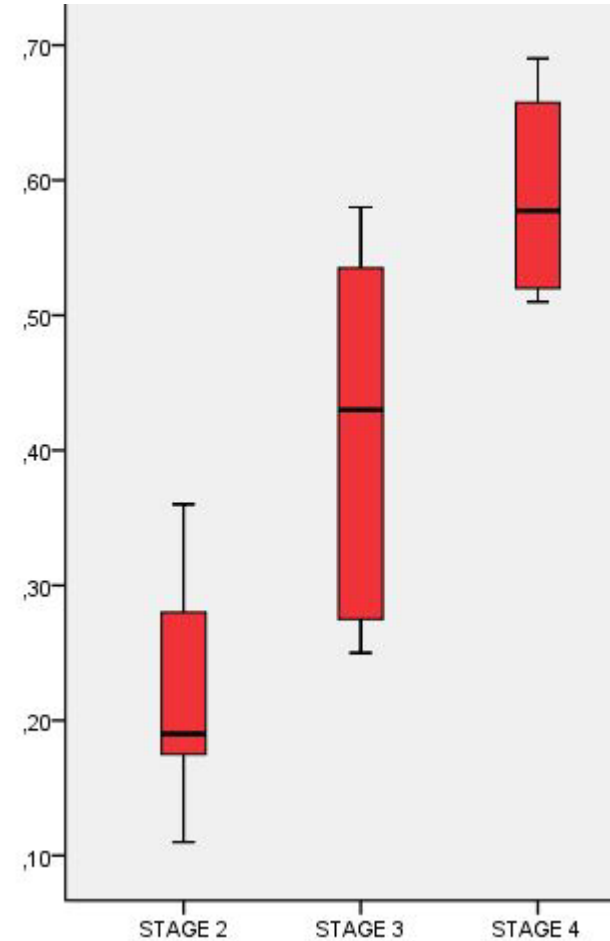
D50



MITOS



KING's



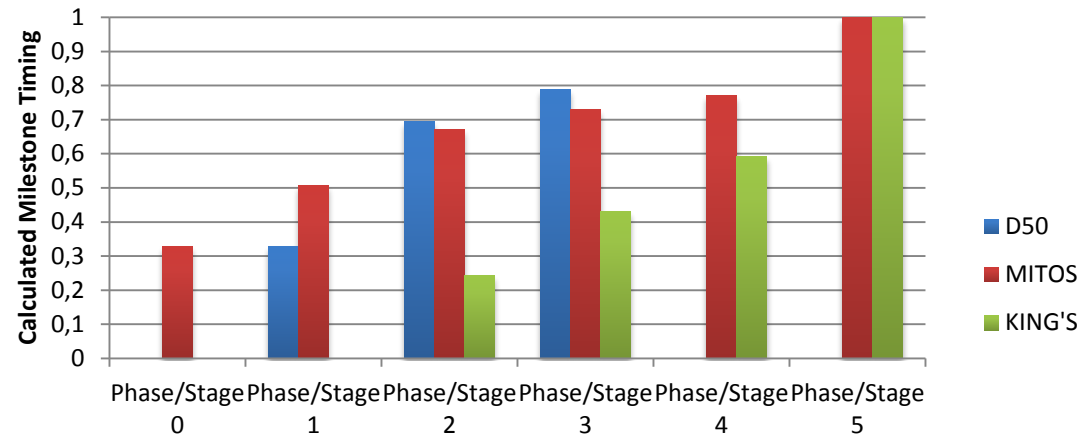
X AXIS: STAGE/PHASE
Y AXIS: MILESTONE TIMING

D50 Phasing and other Contemporary Staging Protocols

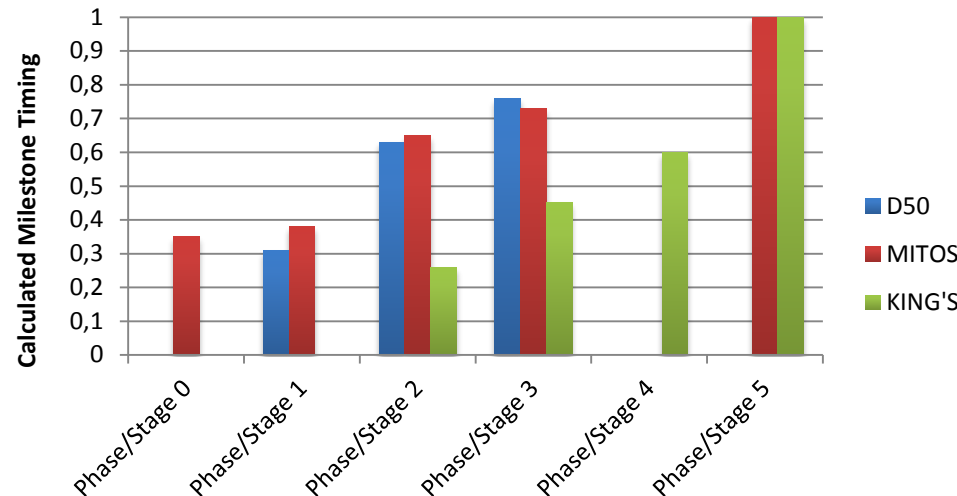
Milestone Timing = Time taken to reach stage from onset/disease duration

0 = symptom onset
1 = death

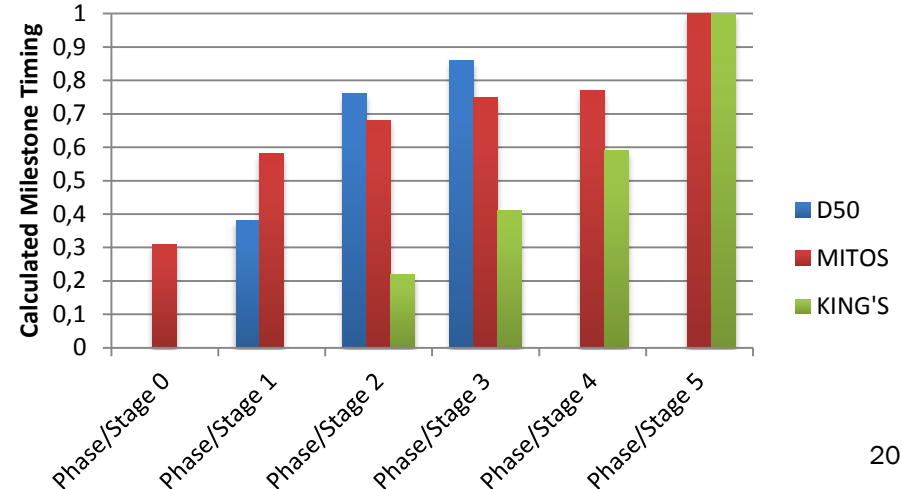
Mean Milestone Timings for Different Staging Systems: Full Cohort (n = 20)



Mean Milestone Timings for Different Staging Systems: Fast Progressors (n = 10)



Mean Milestone Timings for Different Staging Systems: Intermediate Progressors (n = 10)



References

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

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

<https://www.ncbi.nlm.nih.gov/pubmed/20532545>

KINGs

MITOS

