Bayesian Disease Progression Modeling in Clinical Trial Design

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Berry Consultants

DIA BSWG KOL

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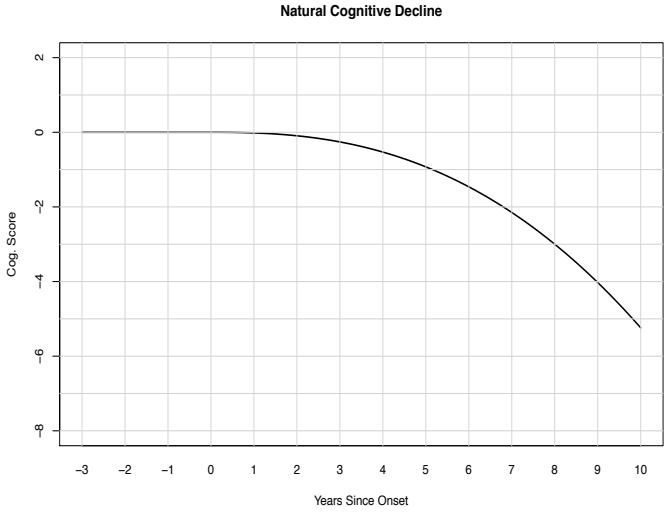
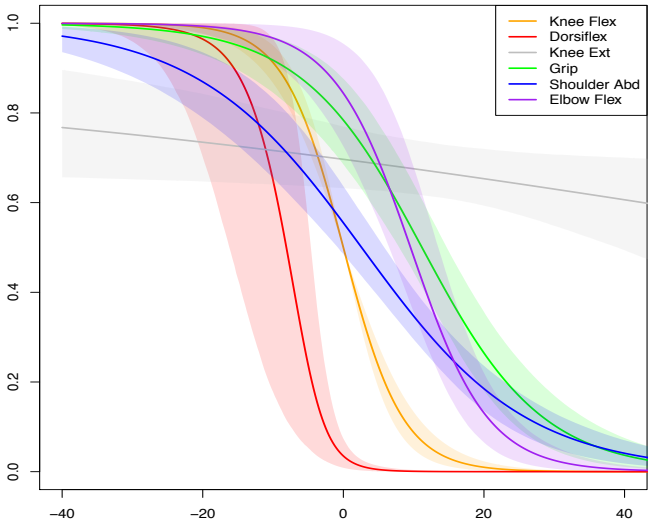
What is a Disease Progression Model?

- Mathematical function that captures quantitatively how an individual evolves over the course of a disease in terms of a single or multiple disease-specific biomarkers and/or clinical outcome measures
  - Likely Monotonic
  - Ideally measures are modeled as a function of "disease age" / stage
  - Single measure vs. joint model over multiple measures (different stages may involve different measures)





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DPM Uses in Clinical Trial Design

- **Virtual Patient Simulator**: Patient simulator for clinical trial design
  - Answer Key Design Questions
  - Pick primary endpoints / outcome measures – what measures that are sensitive enough to capture progression over the course of the trial
  - Understand likely progression of control patients – if control patients are not expected to progress over the course of the trial there is no way to differentiate treatment from control
  - Power given N; length of follow-up; disease subtypes enrolling

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DPM Uses in Clinical Trial Design

- **Primary Analysis Model**: Disease progression modification as a clinical trial endpoint
  - Testing over the time course of the disease instead of at a specific time: Measures at all longitudinal time points add to the estimation of the treatment effect
  - Handles differential length of follow-up: Due to dropout; early interim analyses; extended follow-up
  - More follow-up = Greater power

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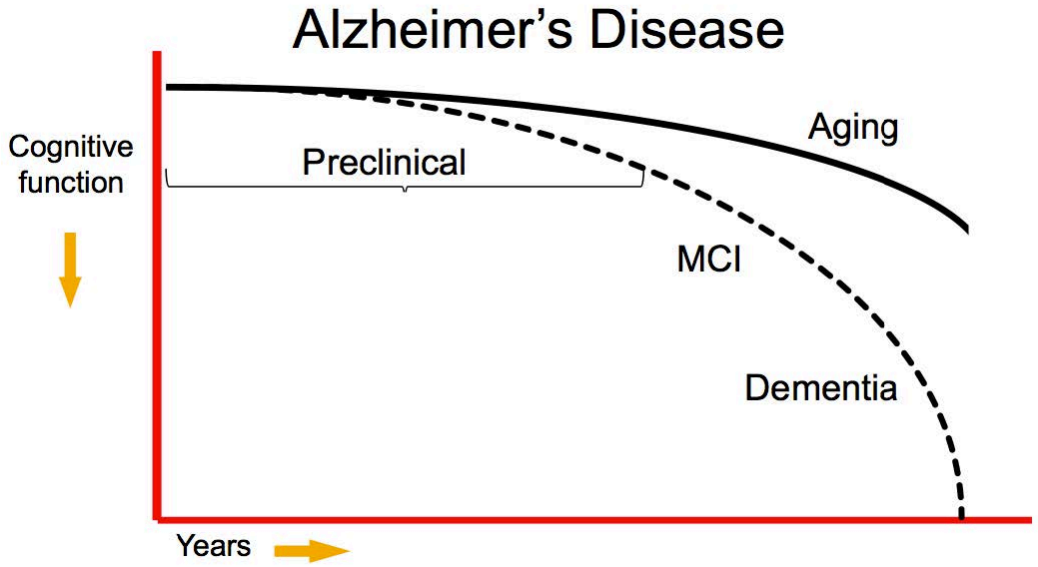
ALZHEIMER'S DISEASE

Alzheimer's Drug Development

- Despite substantial investments new drug development has been massively disappointing
- Current approved therapies do not alter the course of the disease
- New consensus that origin of the disease pathology predates clinical symptoms by over 20 years
- Focus on patients with early or no clinical symptoms



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Alzheimer's Drug Development

- DIAN: Dominantly Inherited Alzheimer Network
  - Rare form of Alzheimer's caused by a gene mutation
  - Early age of onset
  - Provides rare opportunity to enroll preclinical patients that will certainly progress
- EPAD: European Prevention of Alzheimer's Dementia
  - Sporadic AD
  - Focus on identifying high risk, asymptomatic individuals based on range of pathological processes

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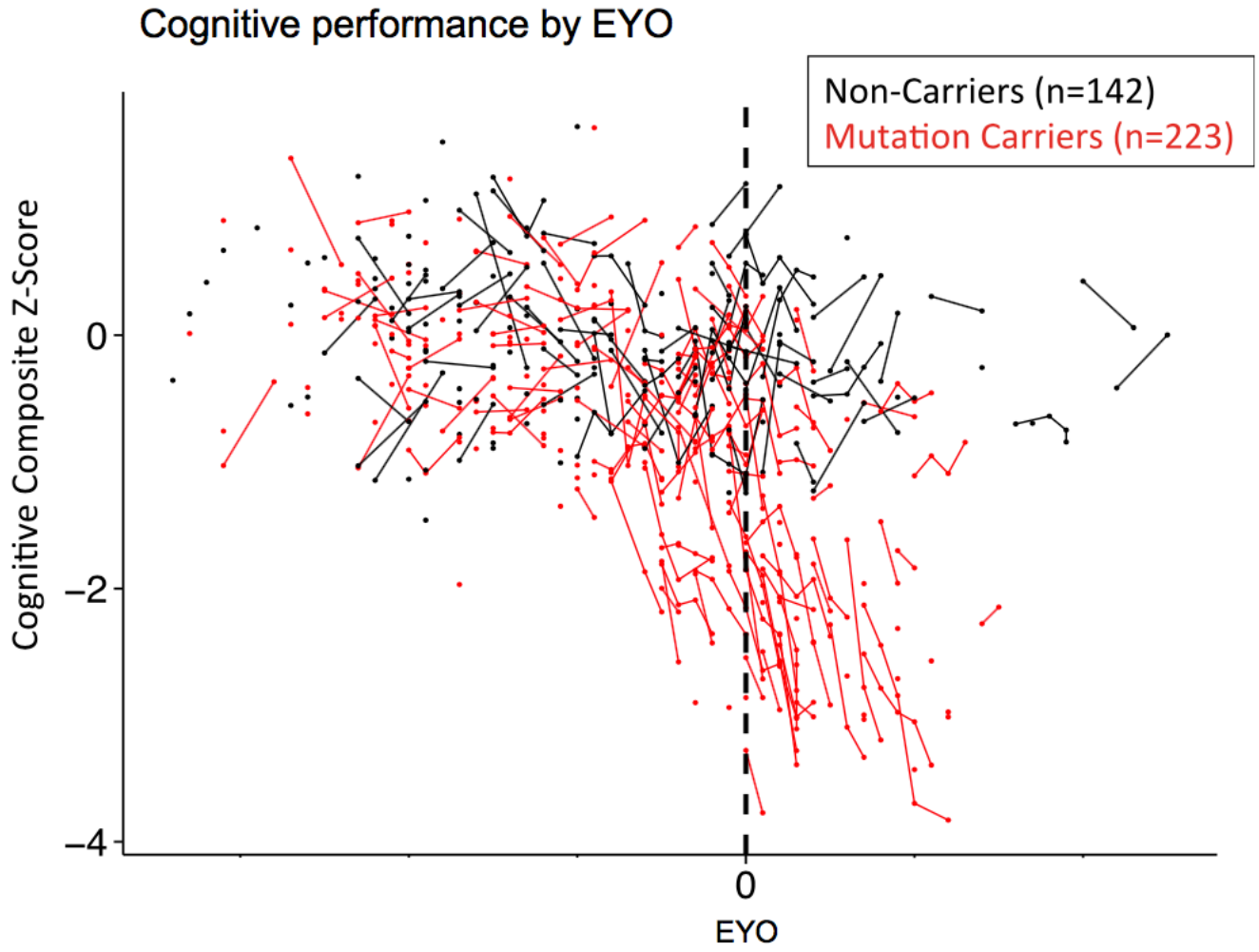
UNDERSTAND NATURAL PROGRESSION

DIAN Observational Data



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DIAN Disease Progression

$$Y_{ij} = \gamma_i + f\left(EYO_{ij} + \delta_i|\alpha\right) + \epsilon_{ij}$$

$$f(x) = \begin{cases} 0 & x \leq -15 \\ (1 + \lfloor x \rfloor - x)\alpha_{\lfloor x \rfloor} + (x - \lfloor x \rfloor)\alpha_{\lfloor x \rfloor + 1} & -15 < x \leq 15 \\ \alpha_{15} & x > 15 \end{cases}$$

- Expected progression as a function of EYO
  - Monotonically decreasing spline with knots at each integer value for EYO between -15 and +15
  - Subject-level random effect for the adjustment in the estimated age of onset (EYO_{ij})
  - Subject-level random effect for the cognitive score at the healthy stage EYO < -15

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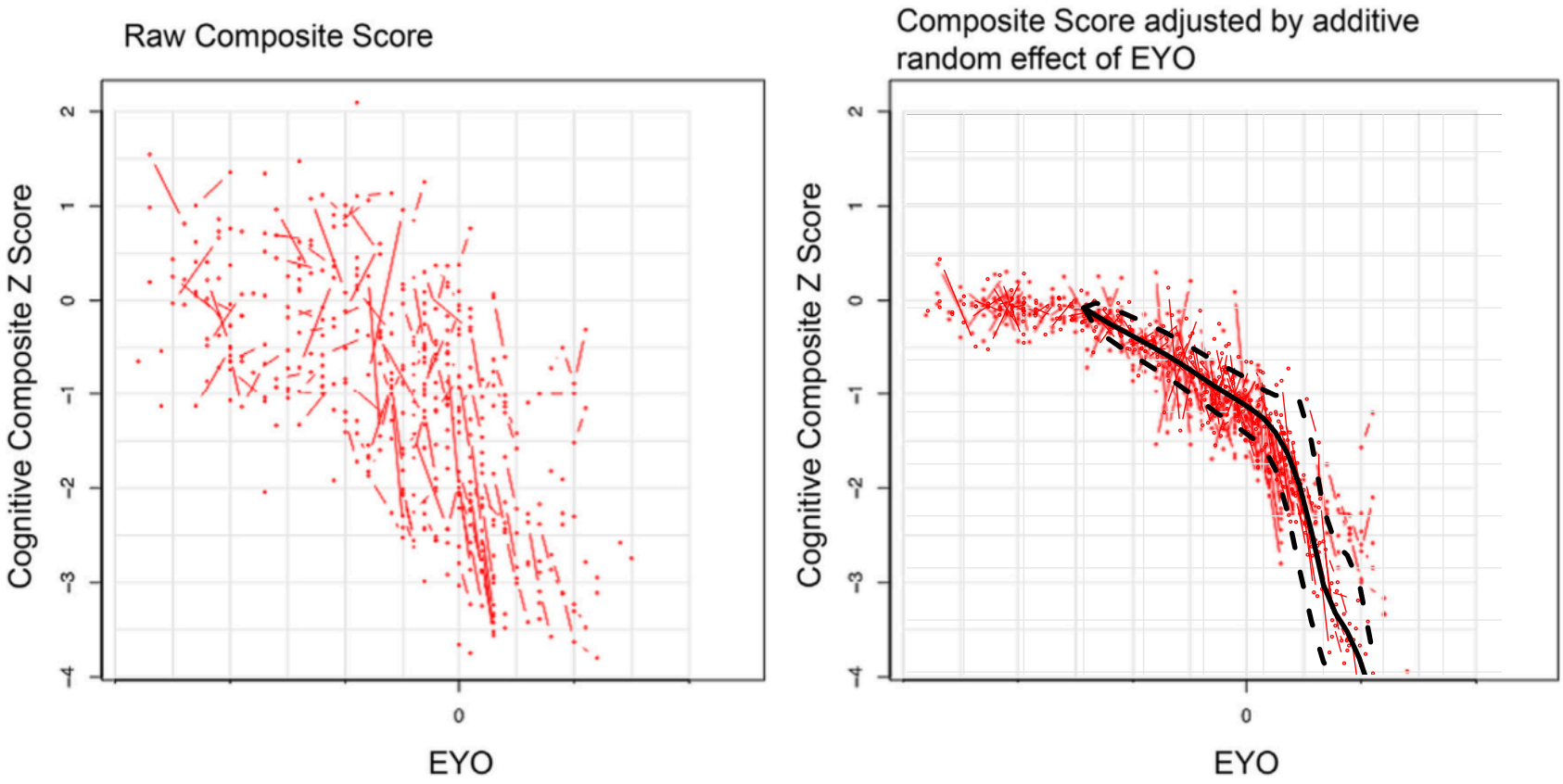
DIAN Disease Progression



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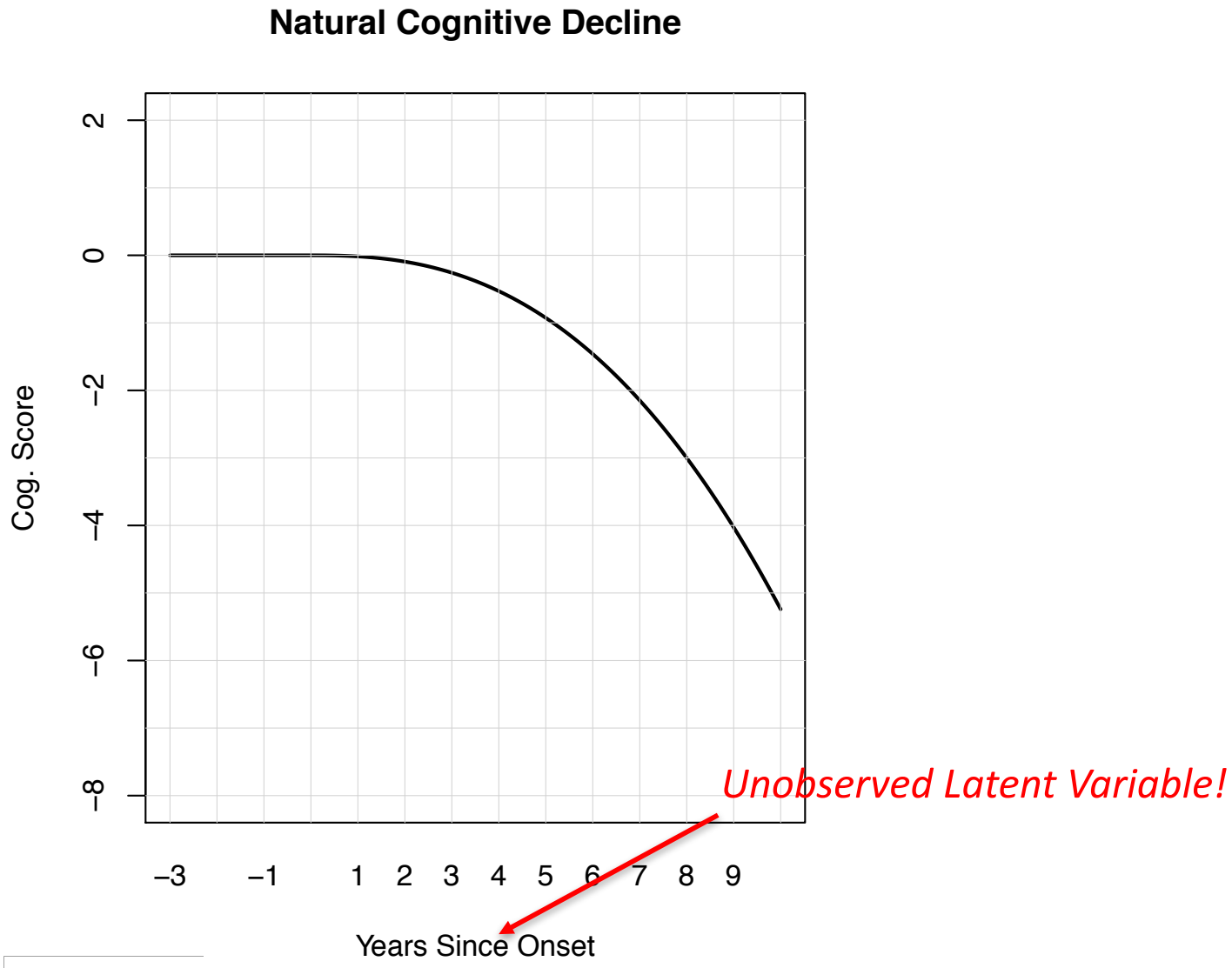
Sporadic AD Disease Progression



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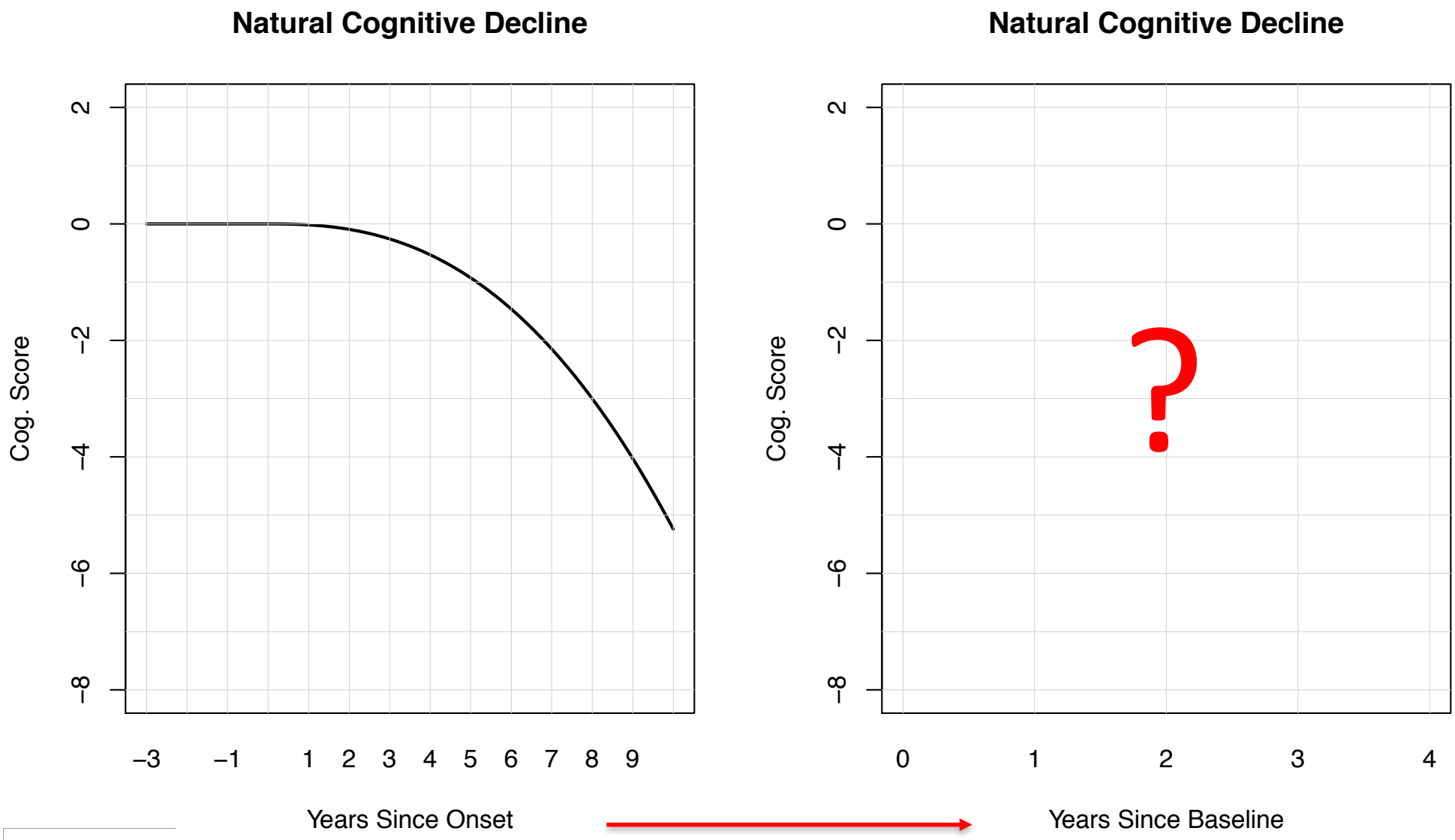

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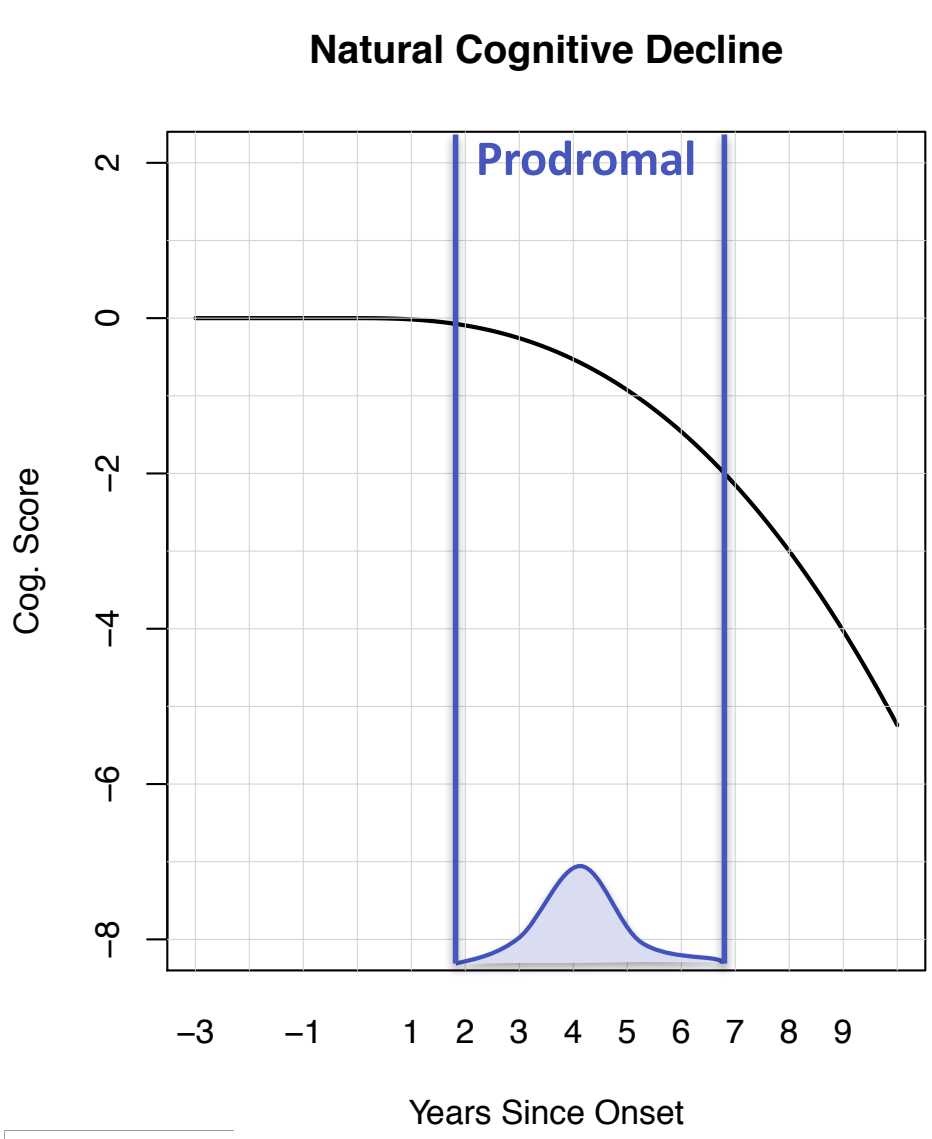

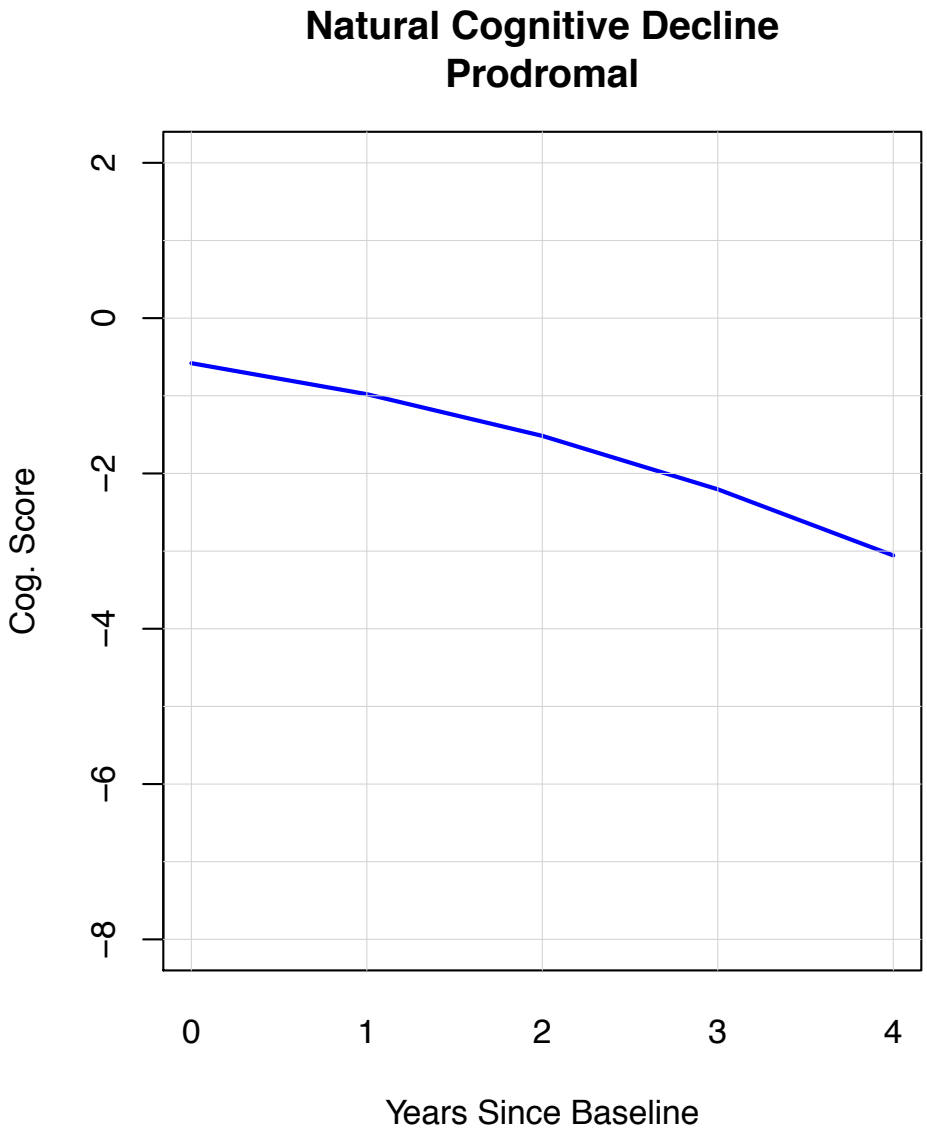

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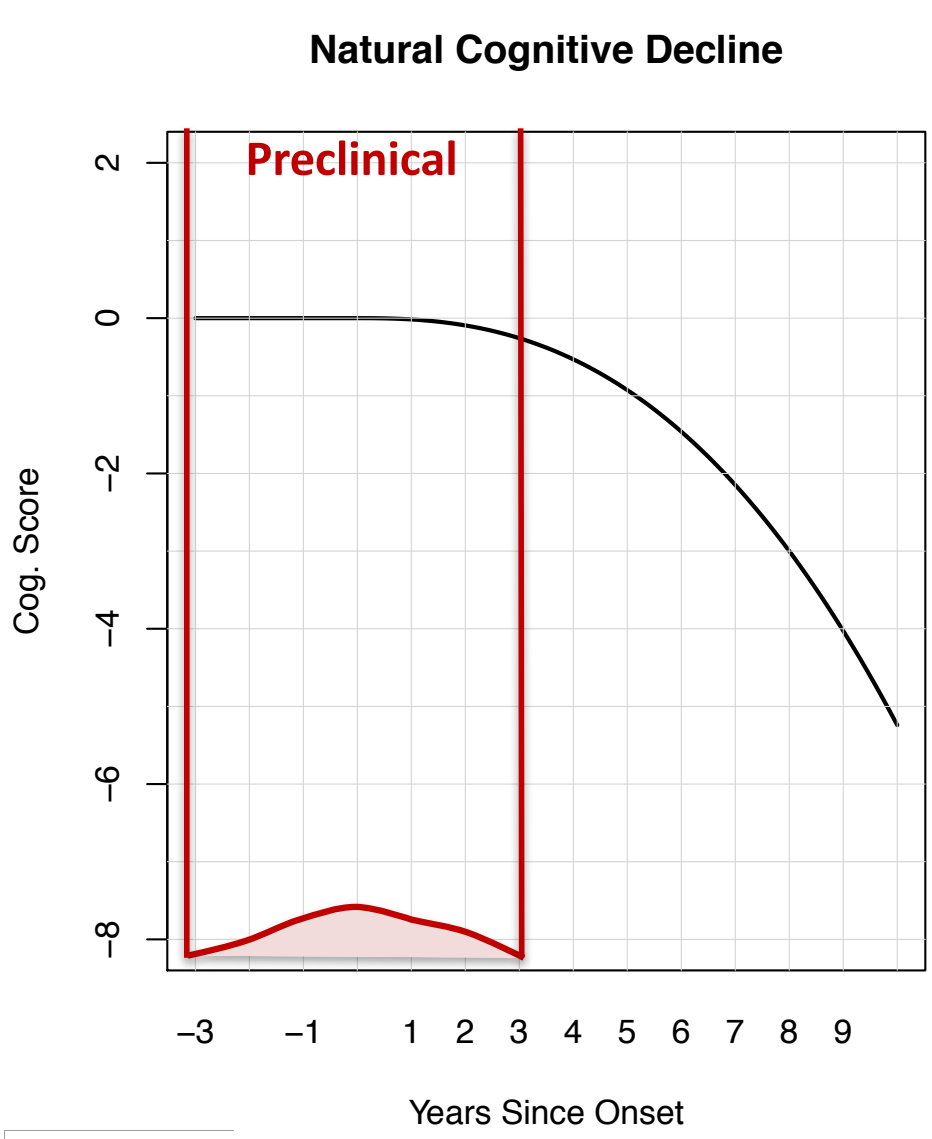

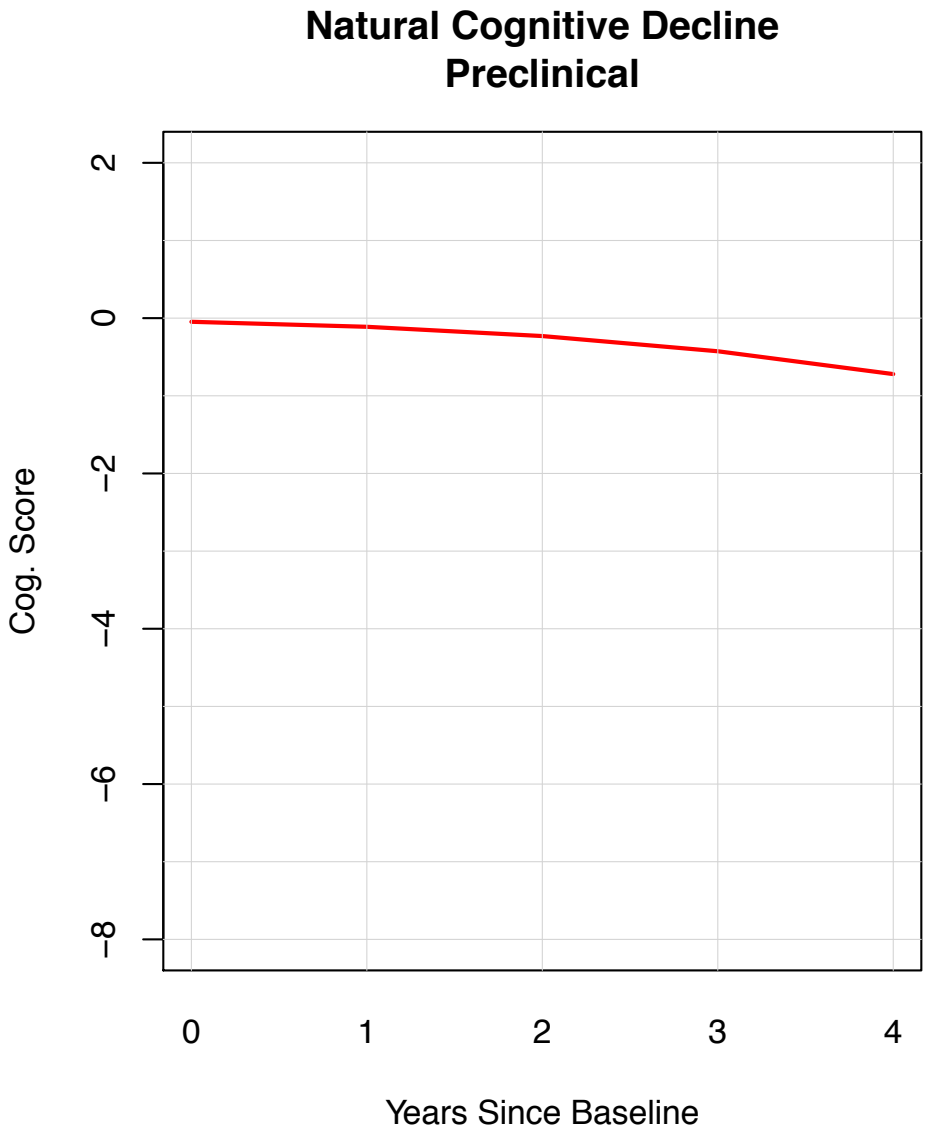

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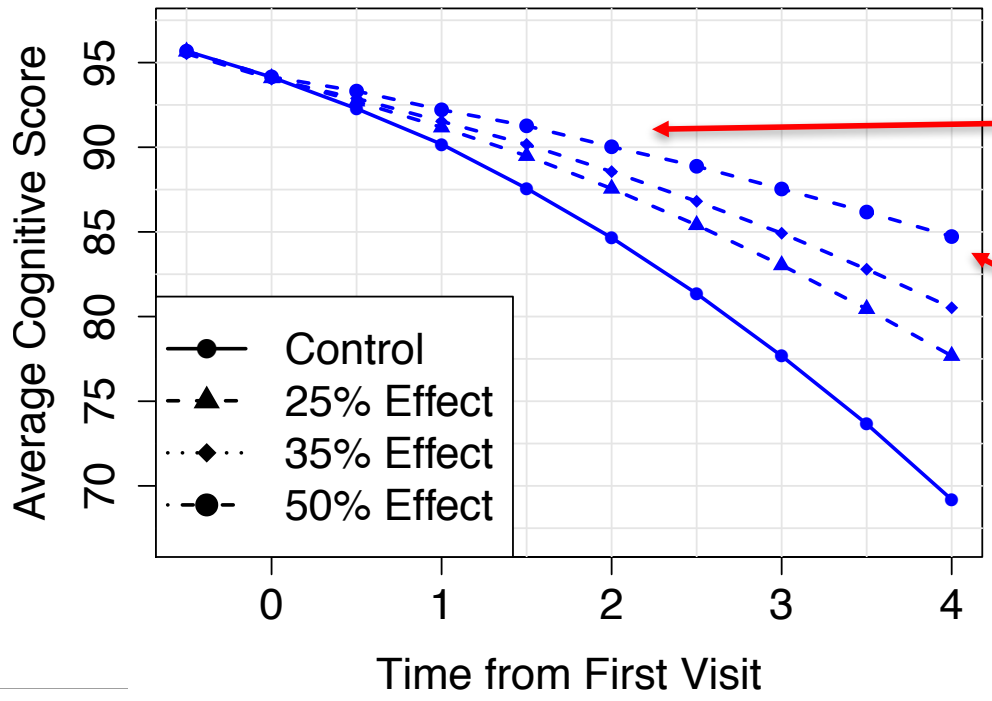
DETERMINE EFFECT OF NOVEL THERAPIES

Incorporation of Treatment Effect

- A disease progression model for measuring the change in the rate of decline over time for a treatment compared to control arm



- Not constant treatment effect!
- Proportional to the expected decline on control
- **2 Years**: Control expected to decline 10 units -> Therapy with 50% effect would decline only 5 units
- **4 Years**: Control expected to decline 25 units -> Therapy with 50% effect would decline only 12.5

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Incorporation of Treatment Effect

- A disease progression model for measuring the change in the rate of decline over time for a treatment compared to control arm

$$Y_{ij} = \begin{cases} \gamma_i + \sum_{v=j}^{-1} \alpha_v + \epsilon_{ij} & j = \cdots, -2, -1 \\ \gamma_i + \epsilon_{ij} & j = 0 \\ \gamma_i + \exp(\theta_{t_i}) \sum_{v=1}^{j} \alpha_v + \epsilon_{ij} & j = 1,2,3 \ldots \end{cases}$$

Control Arm Model:
$\alpha_{-2}, \alpha_{-1}, \alpha_1, \alpha_2, \ldots$

Common Treatment Effect:
Disease Progression Ratio (=1 is control)

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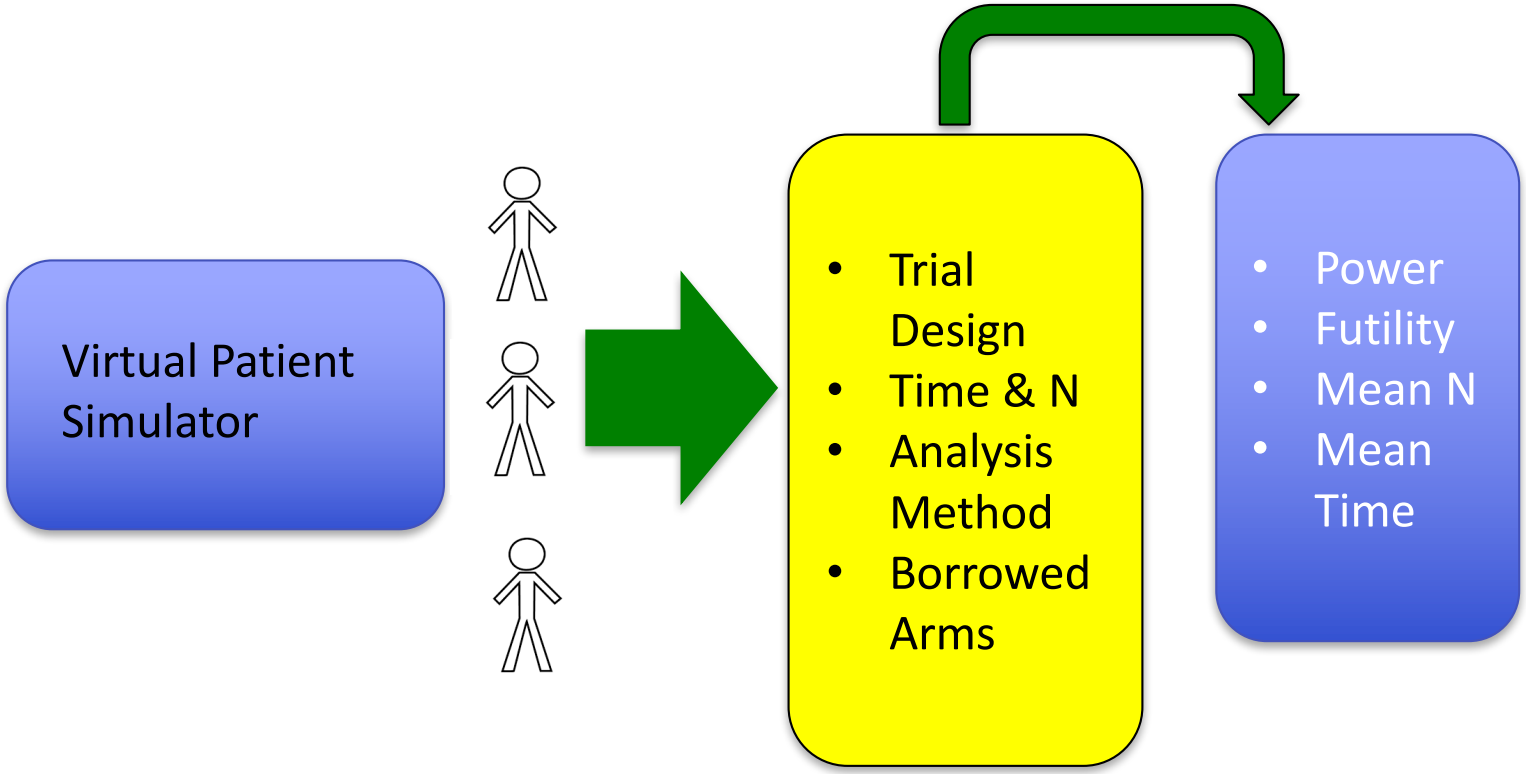
VIRTUAL PATIENT SIMULATOR

Simulating Virtual Subjects



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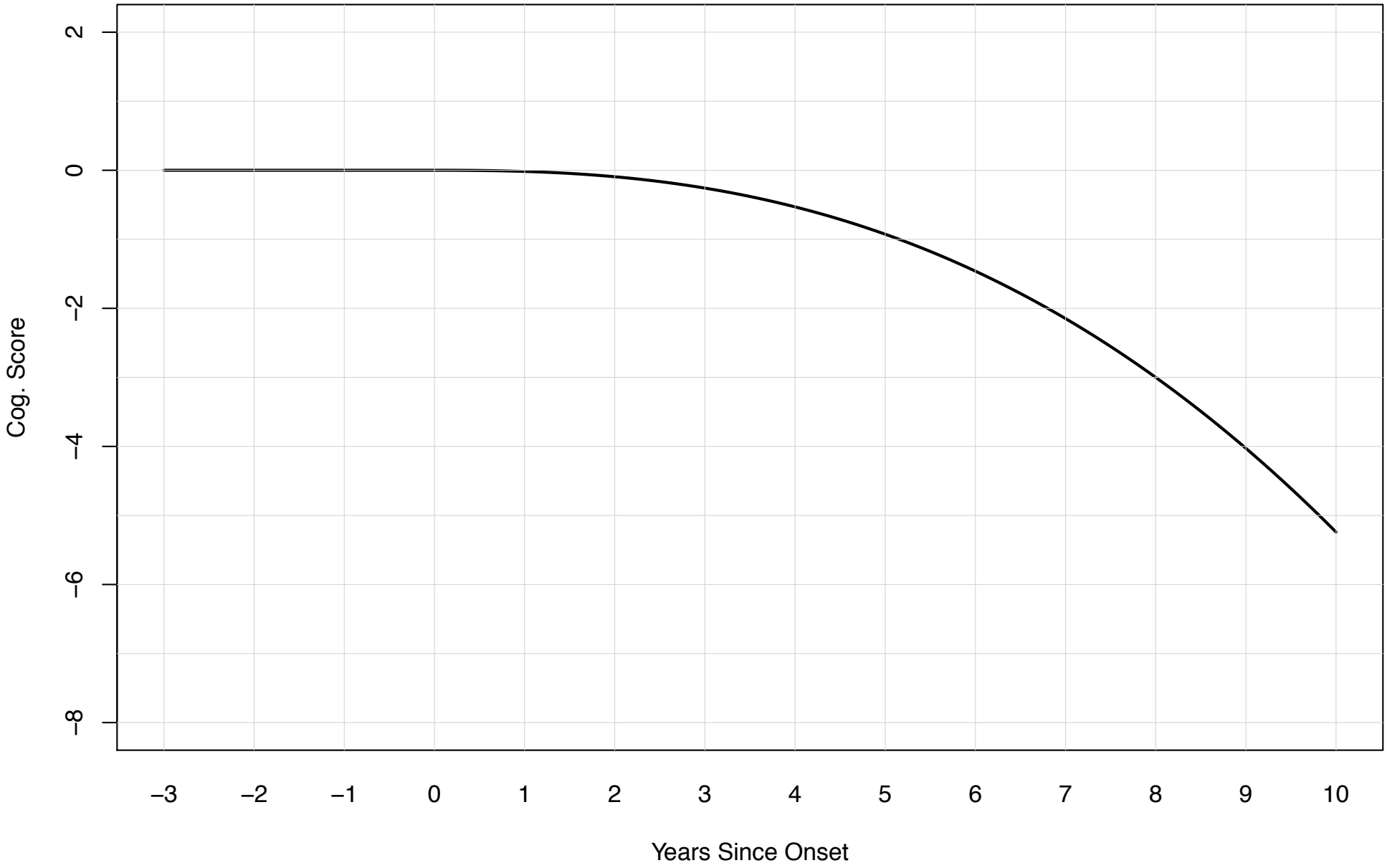
Natural Cognitive Decline



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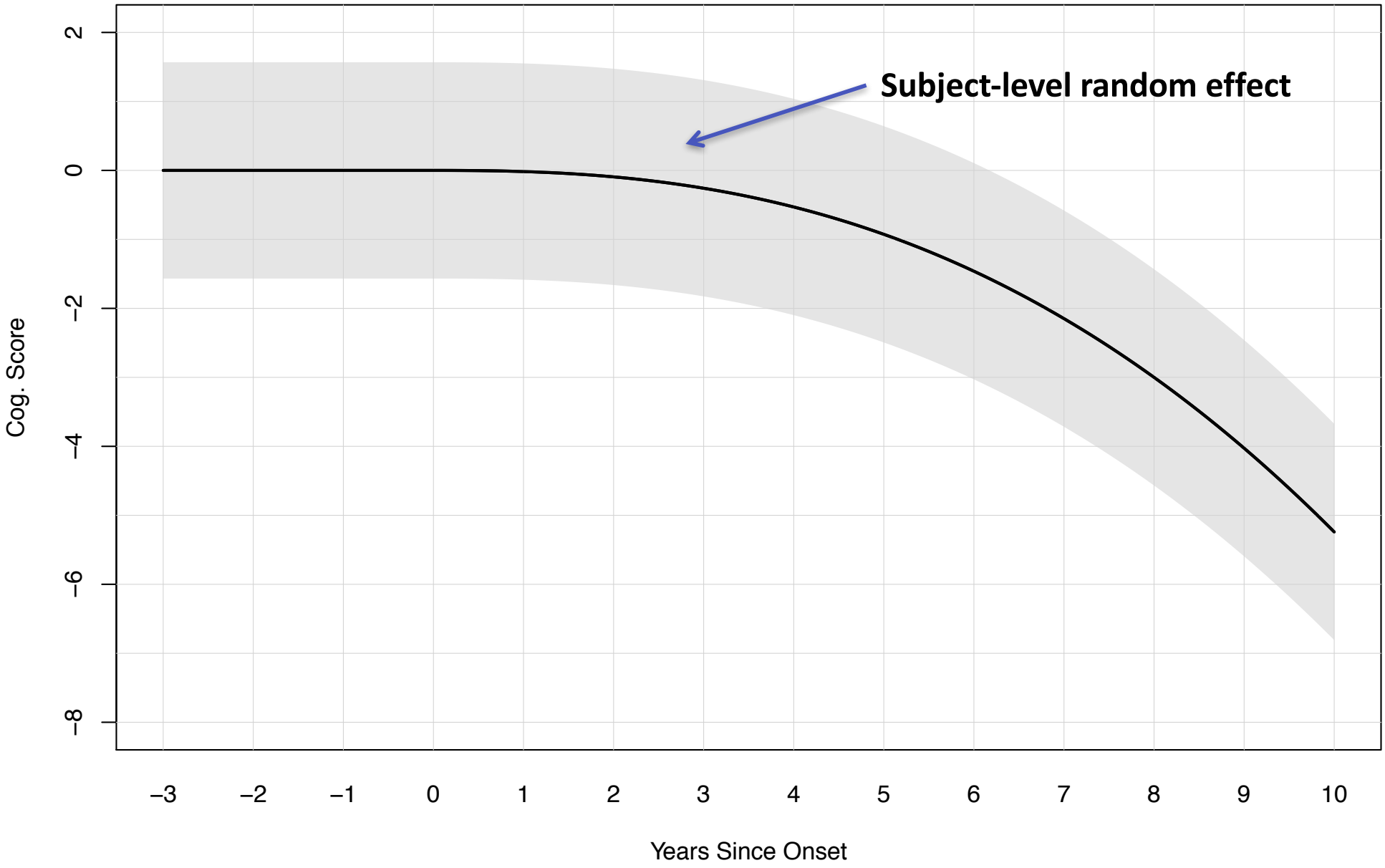
Natural Cognitive Decline
+Subject–Level Random Effect



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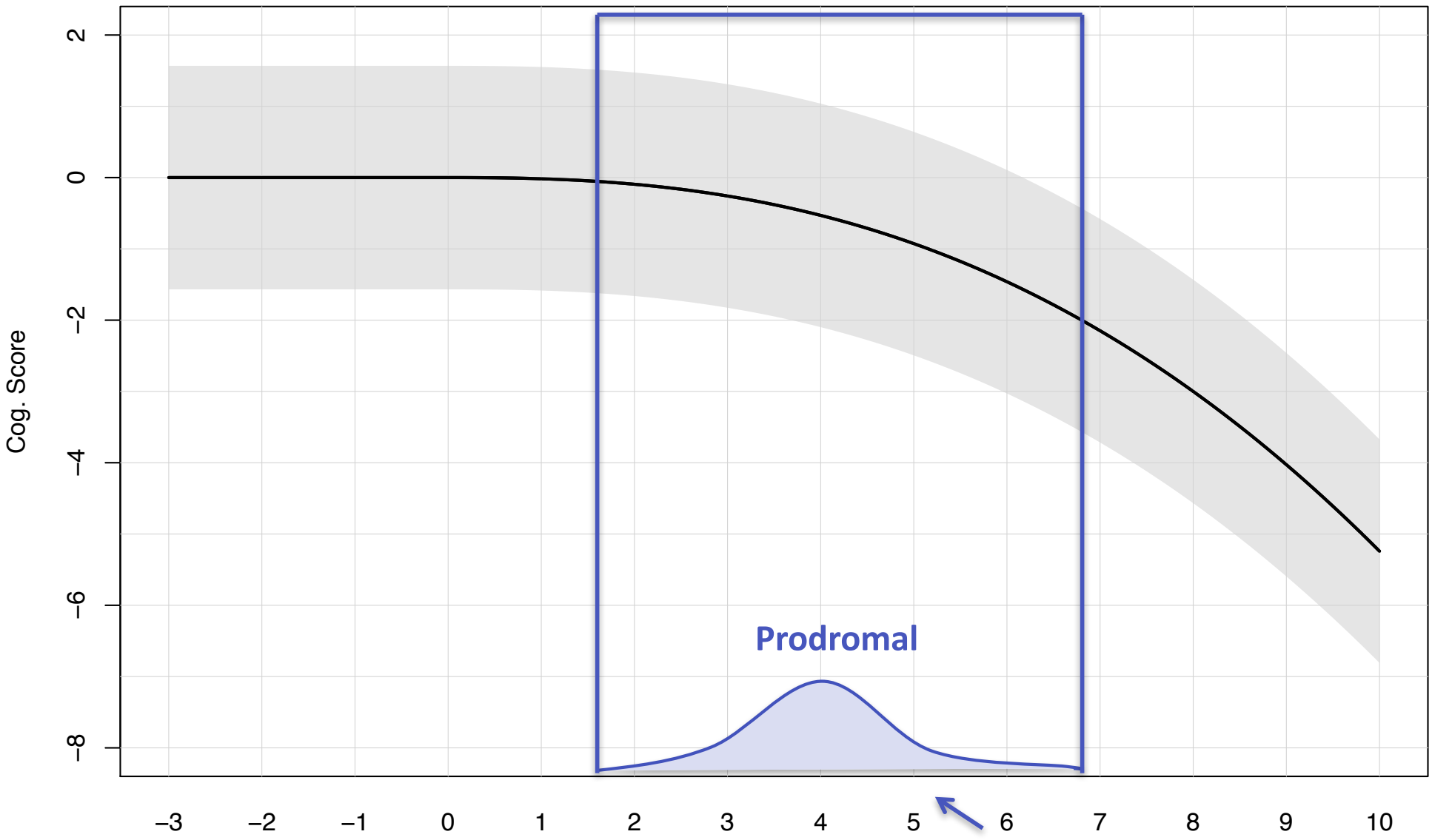

Enroll Subjects with varying years sin onset depending on disease stage

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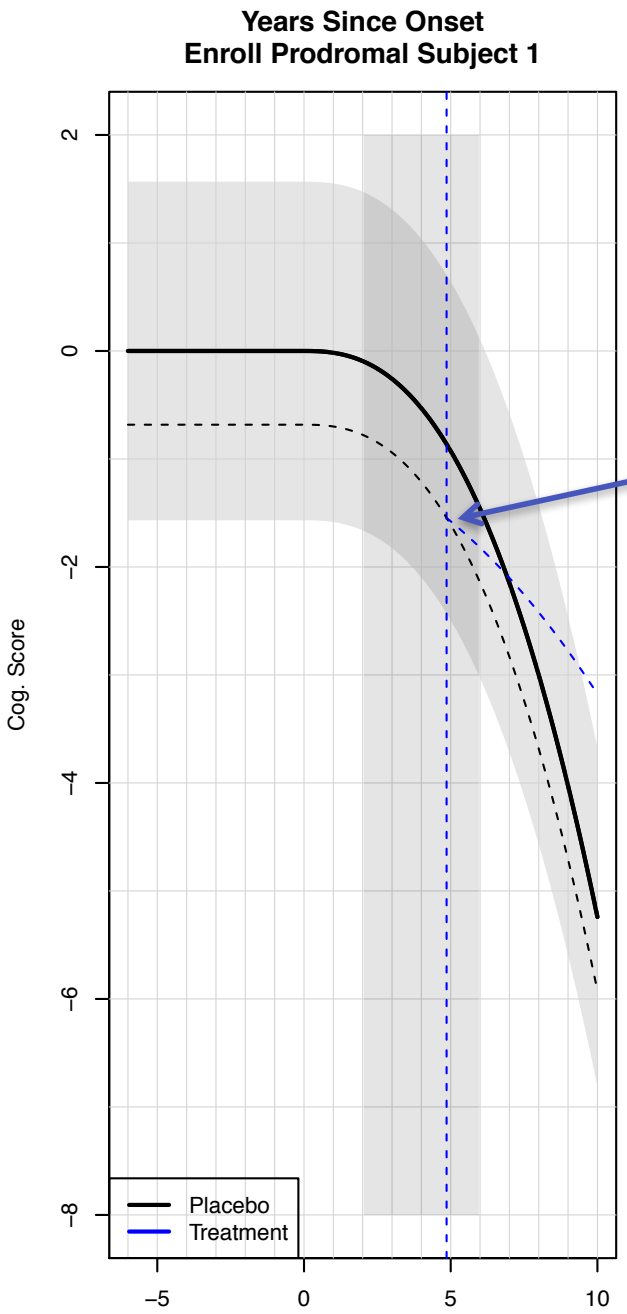

Subject 1:

Subject-level random effect: -.8

Years since onset at enrollment: 5

Enrolled to treatment group

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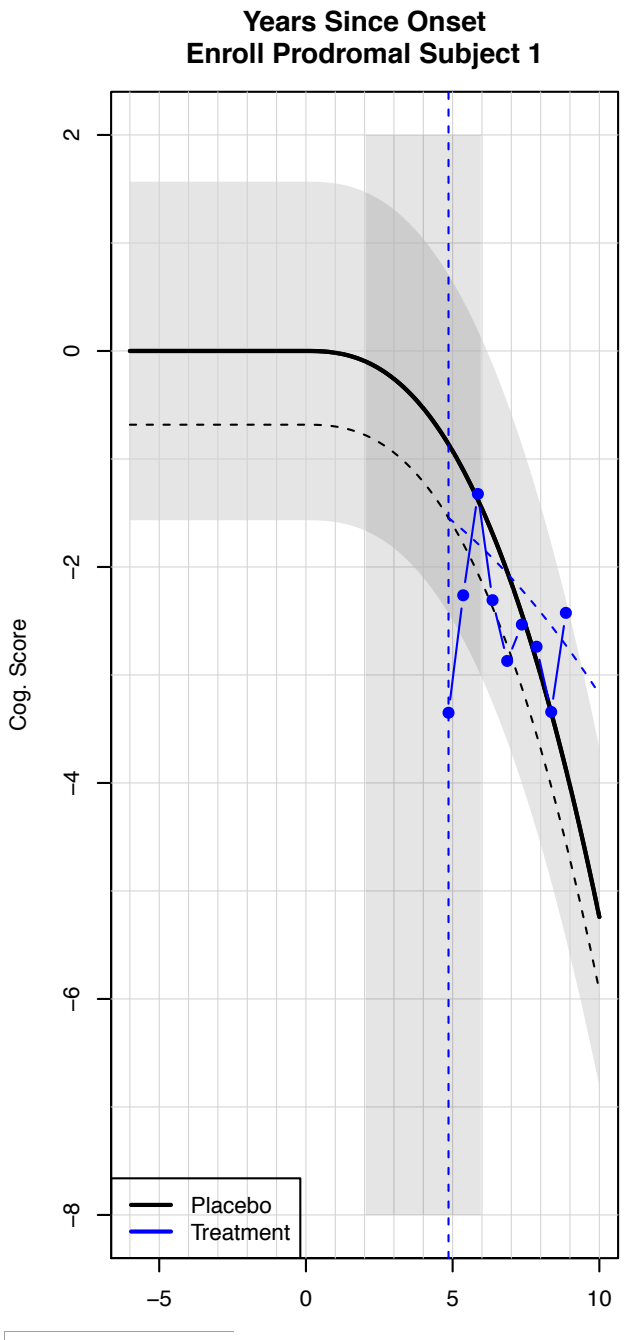

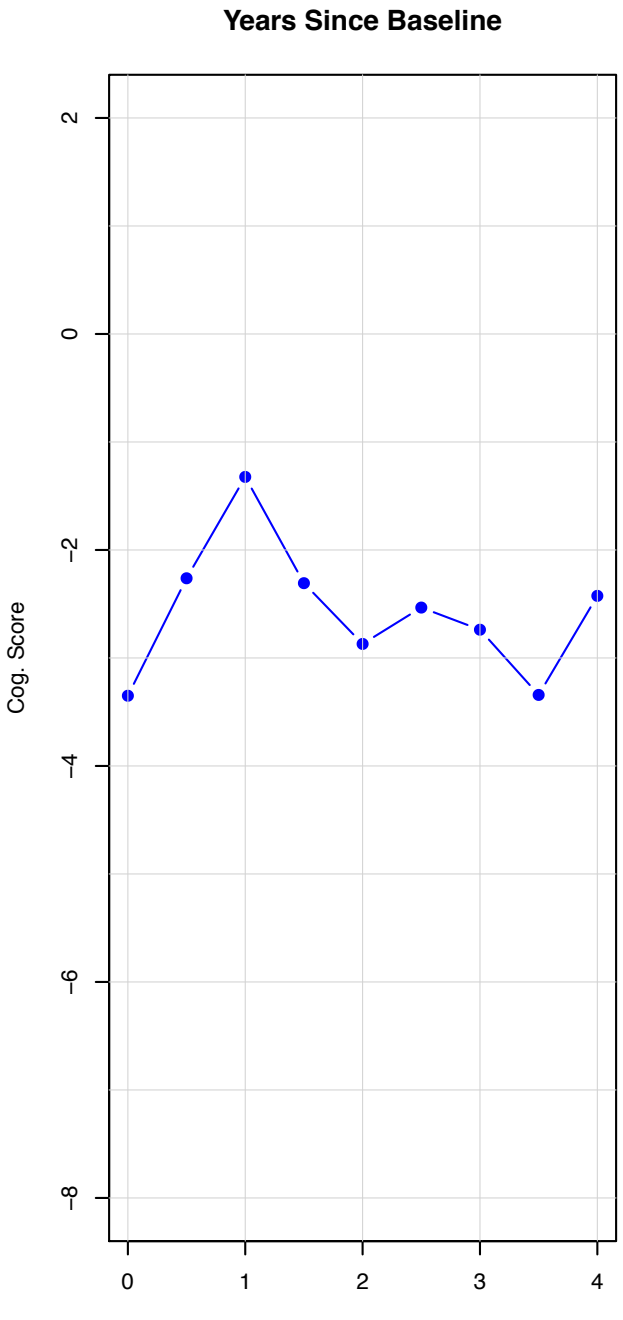

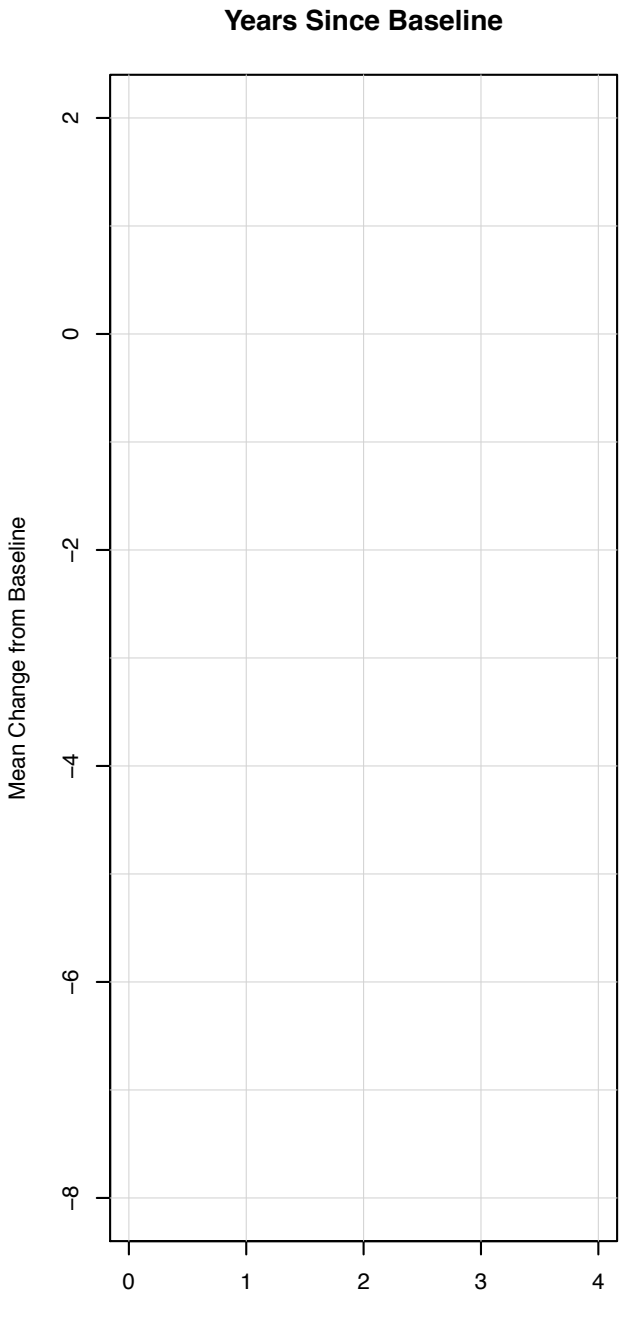

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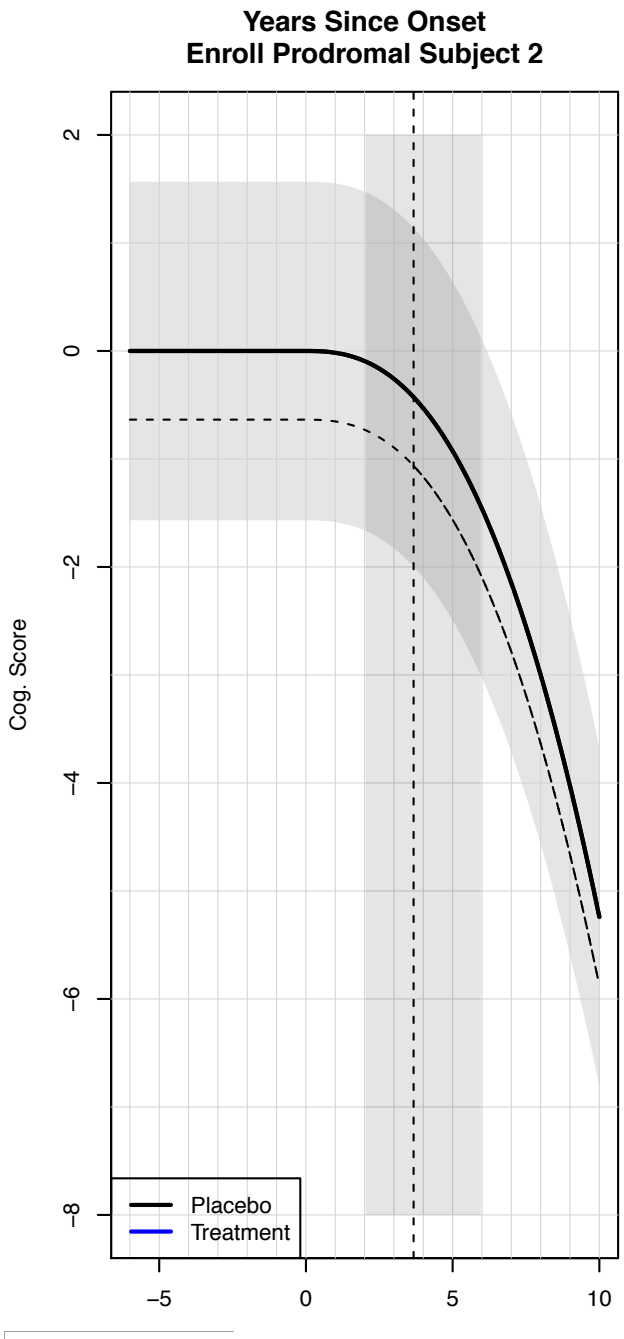

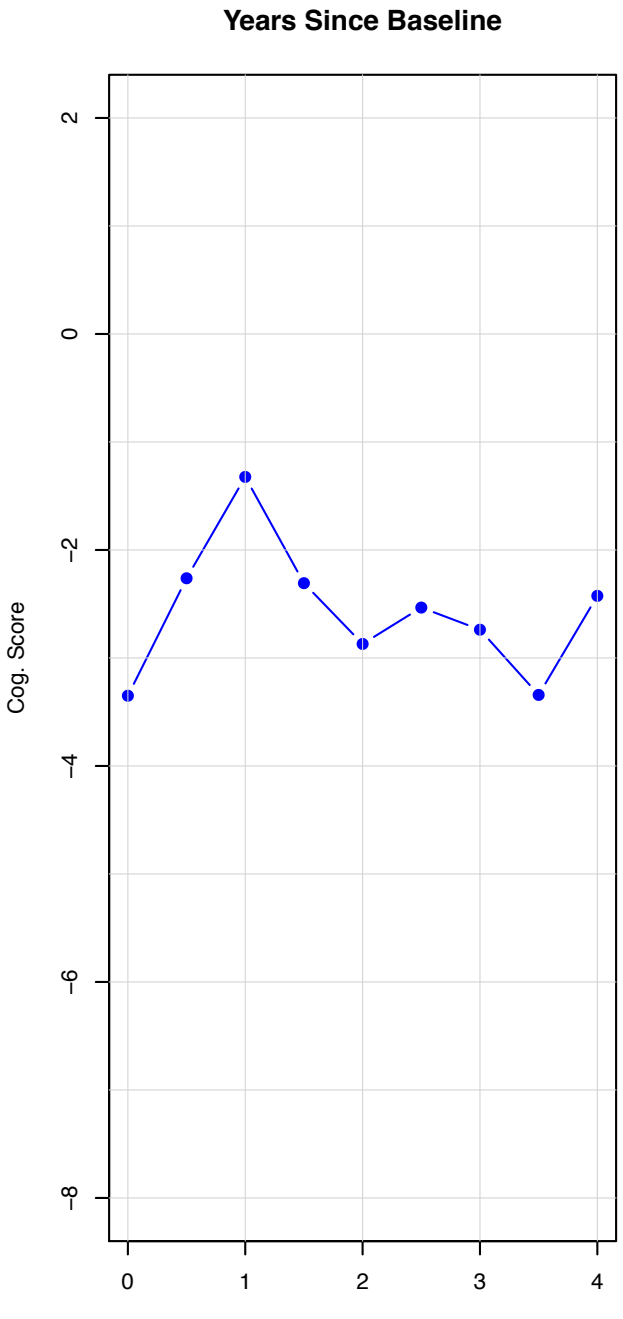

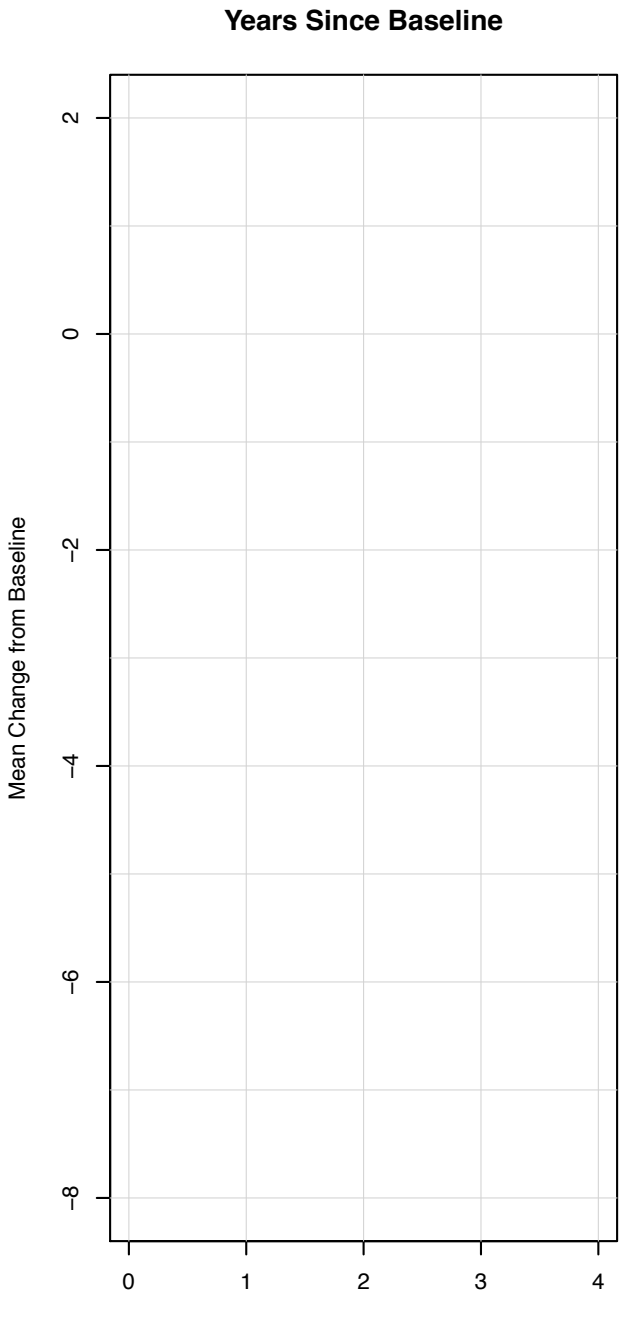

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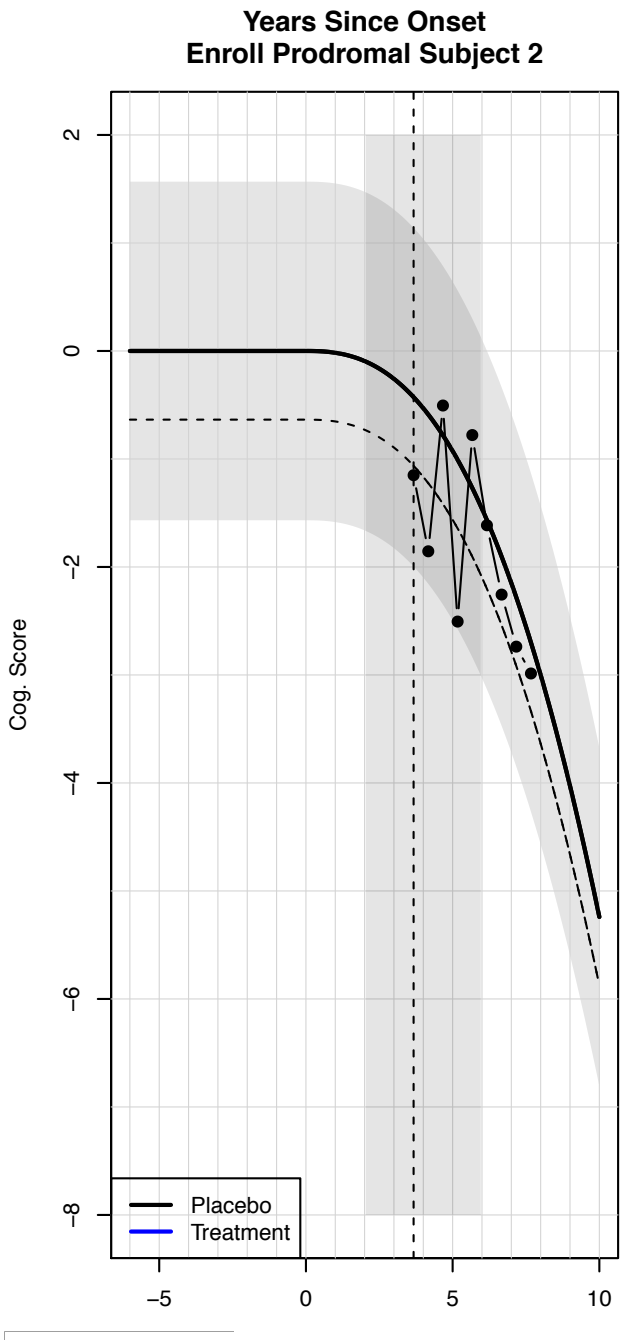

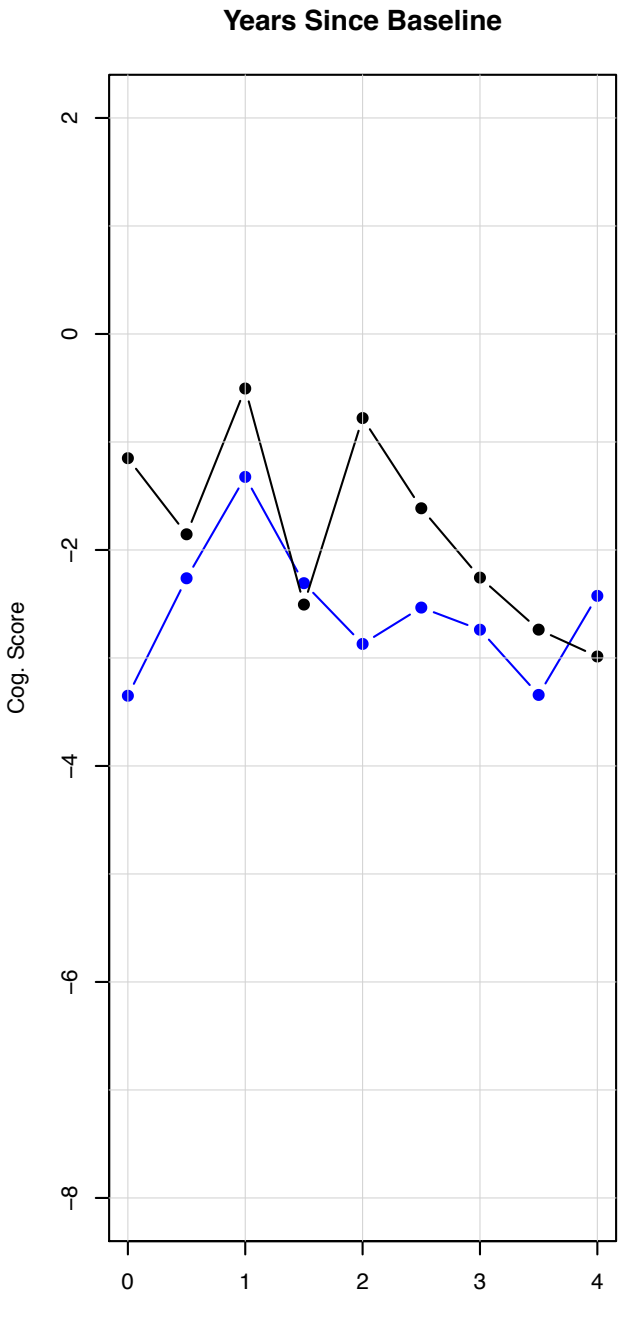

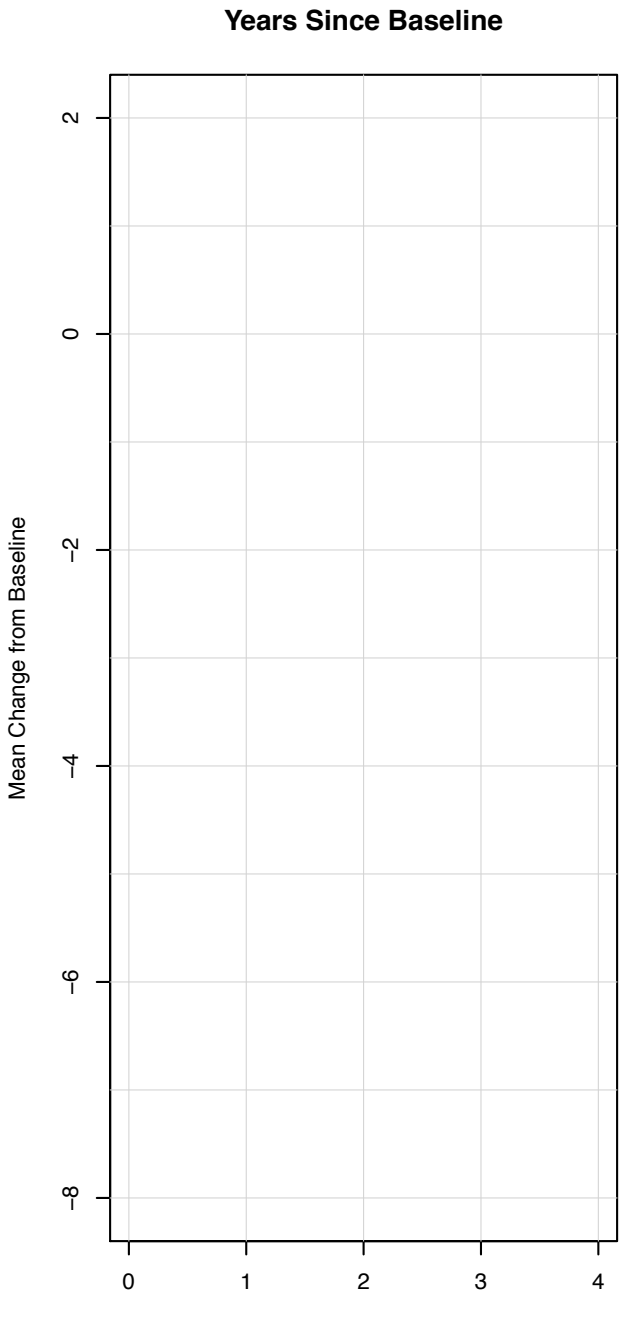

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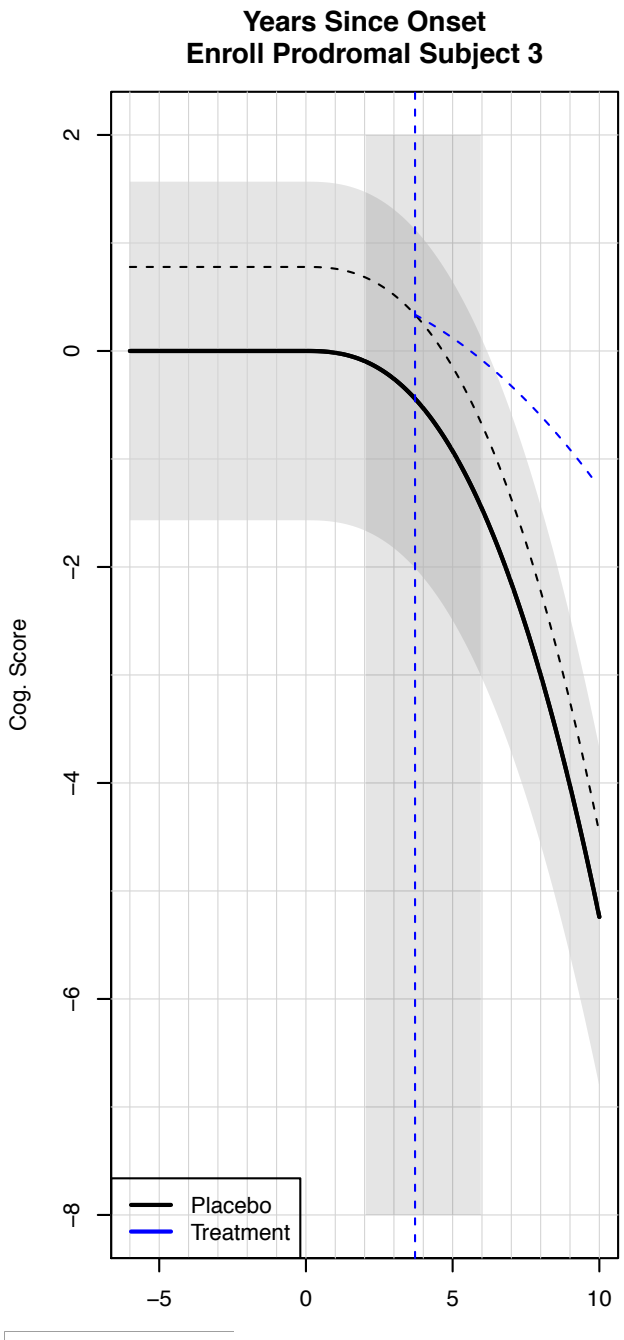

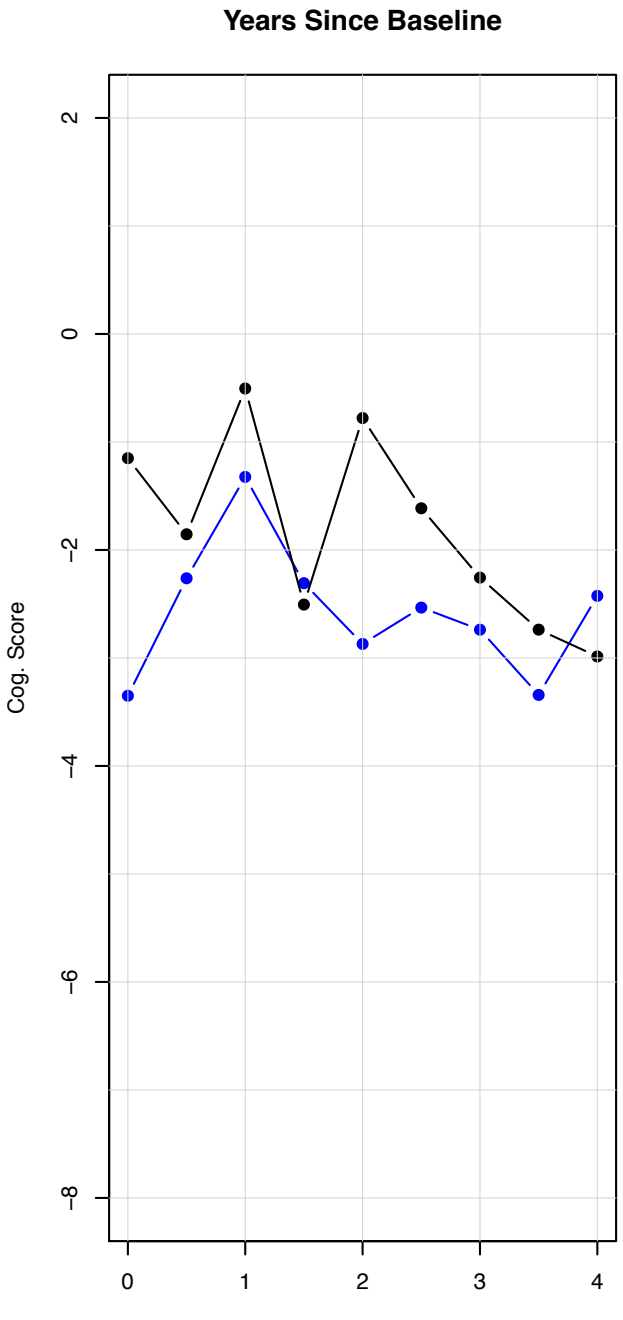

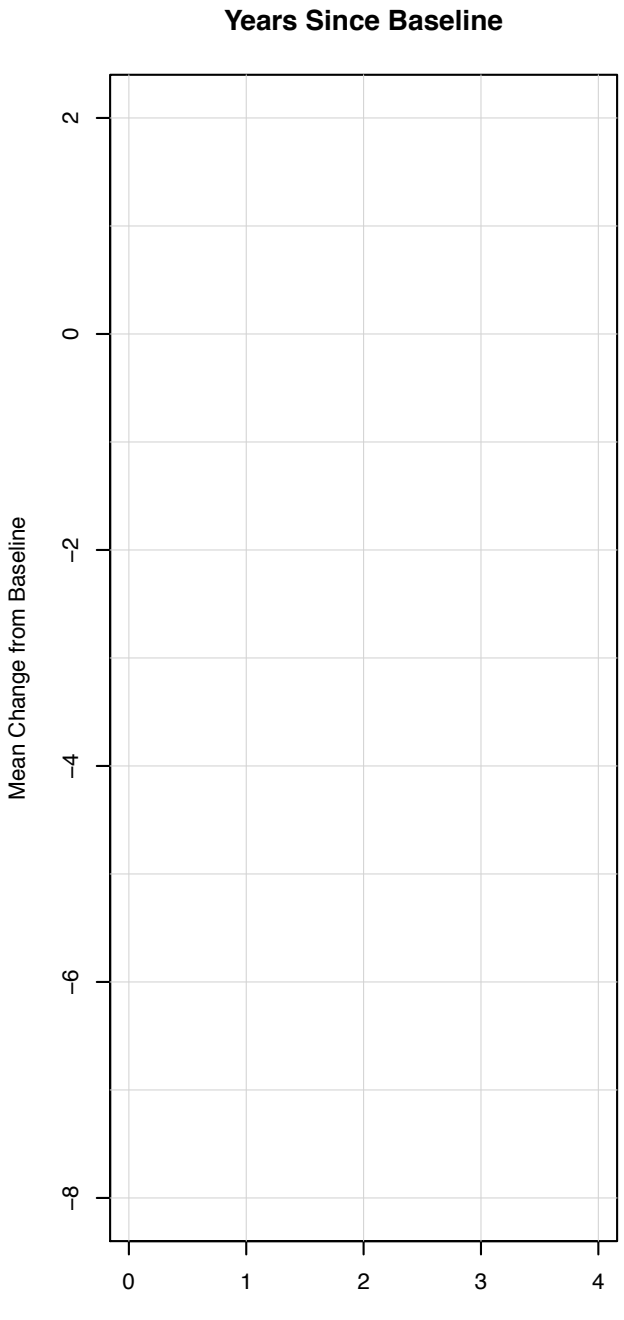

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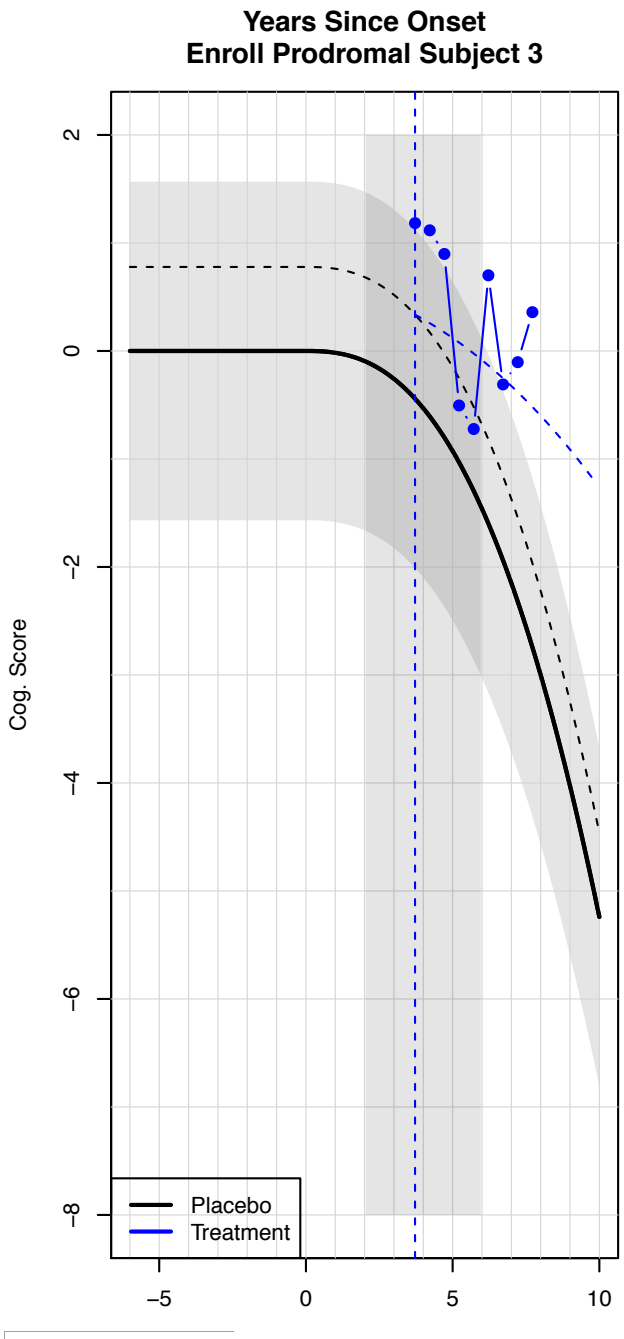

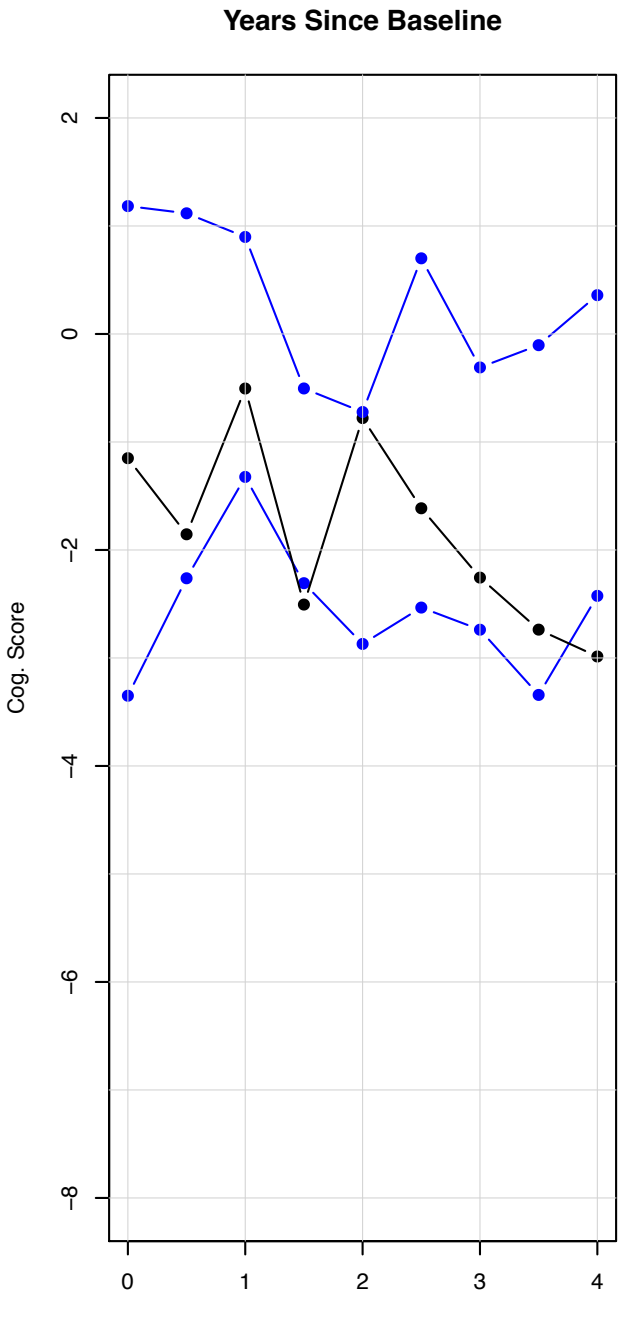

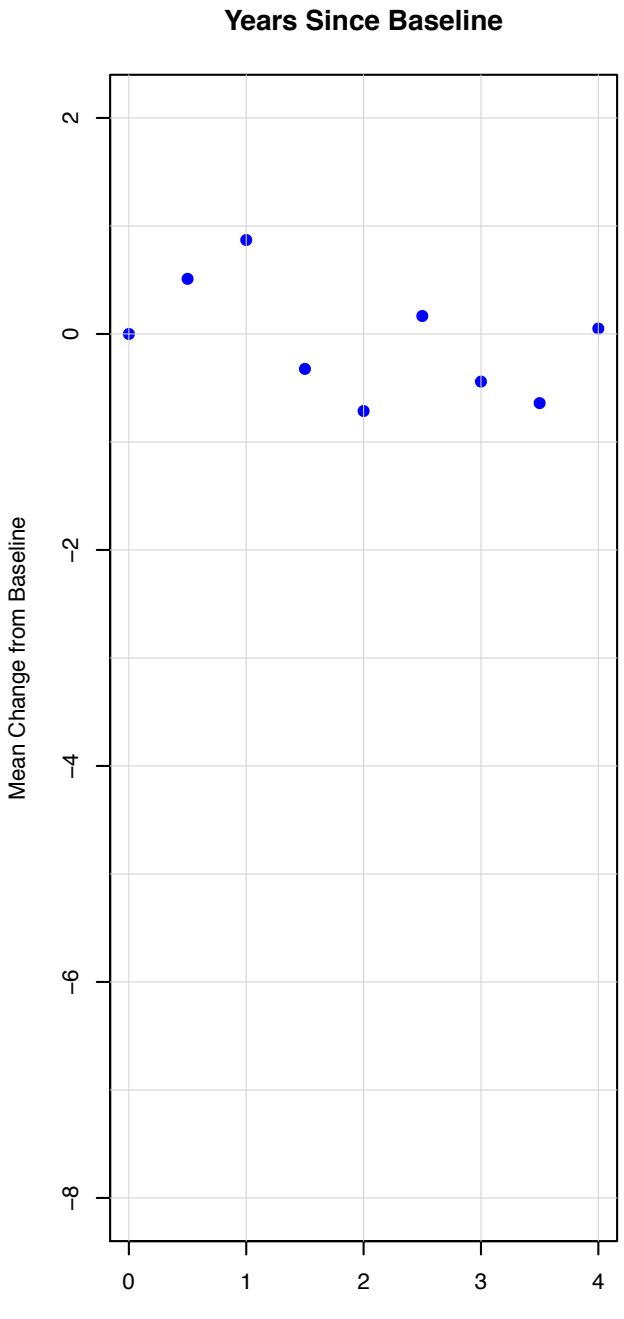

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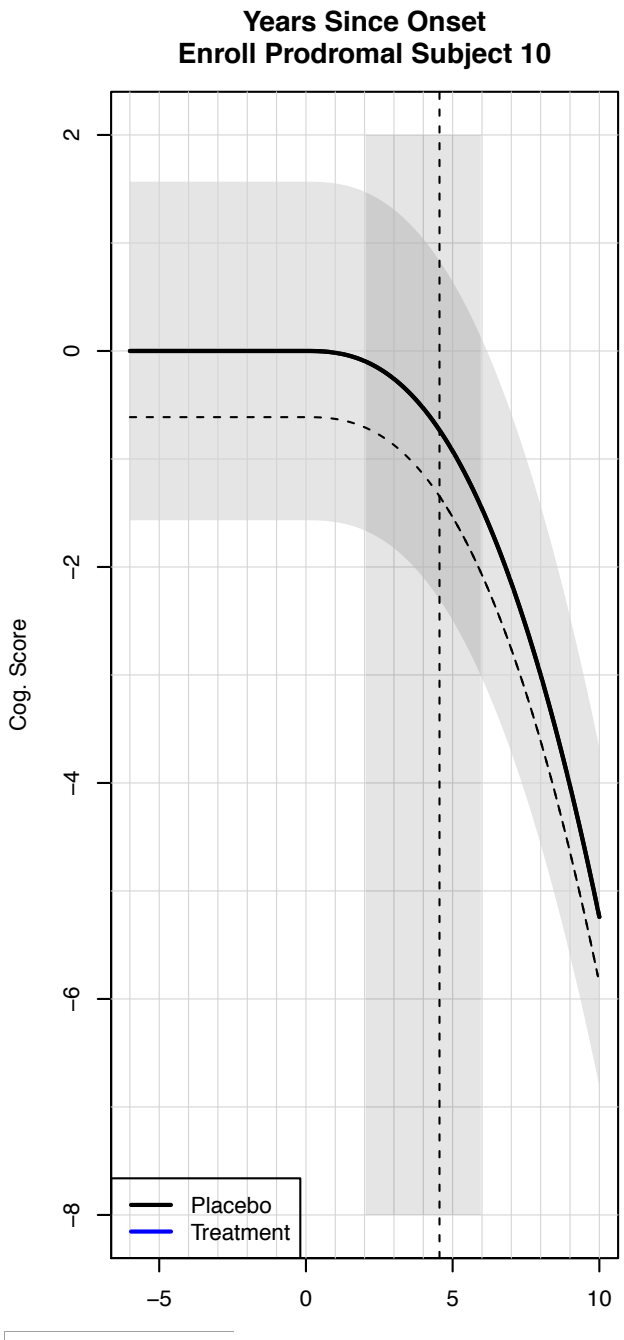

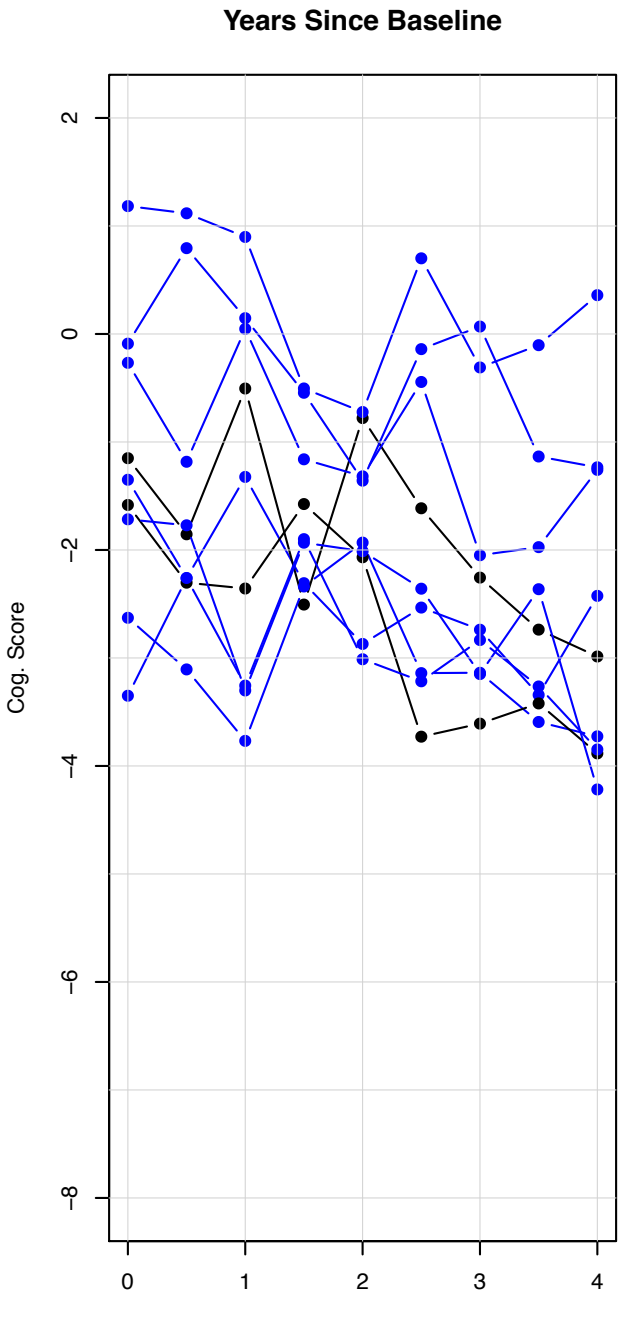

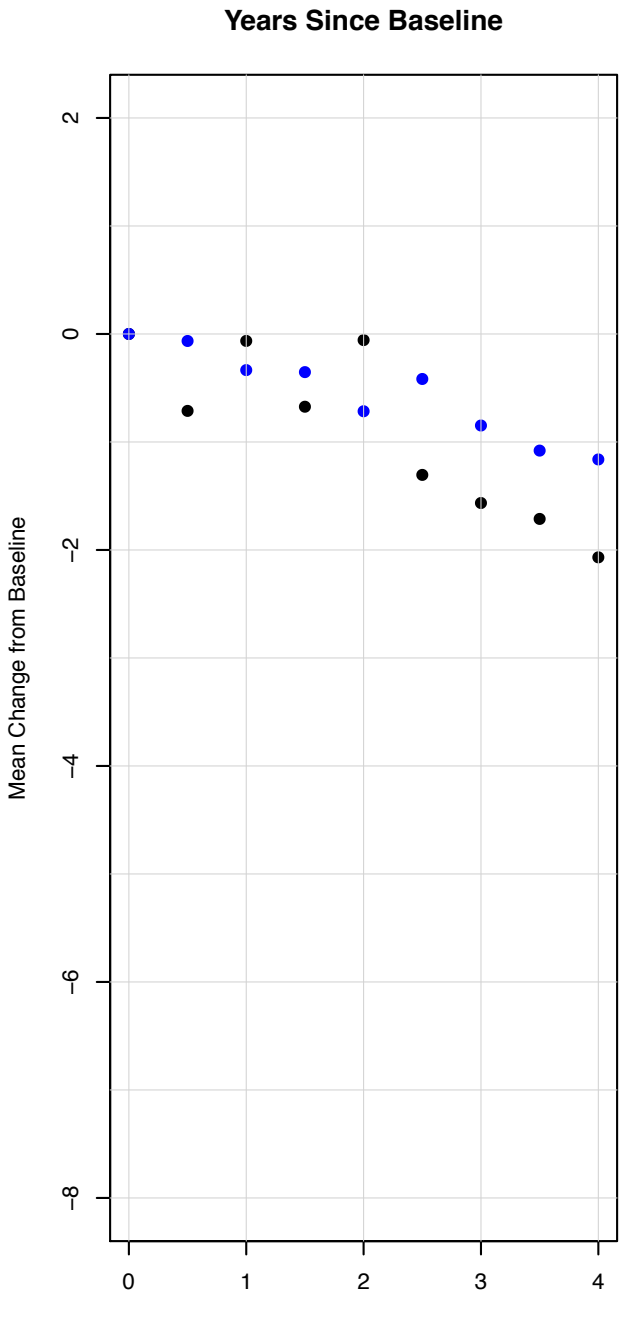

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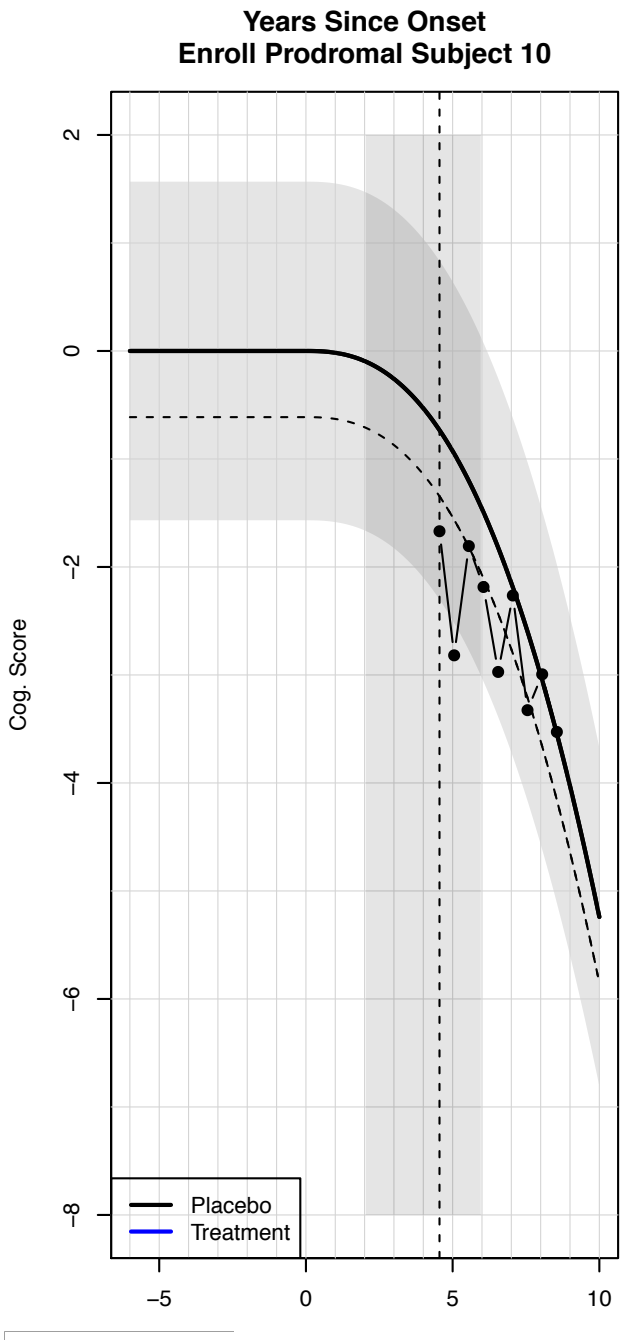

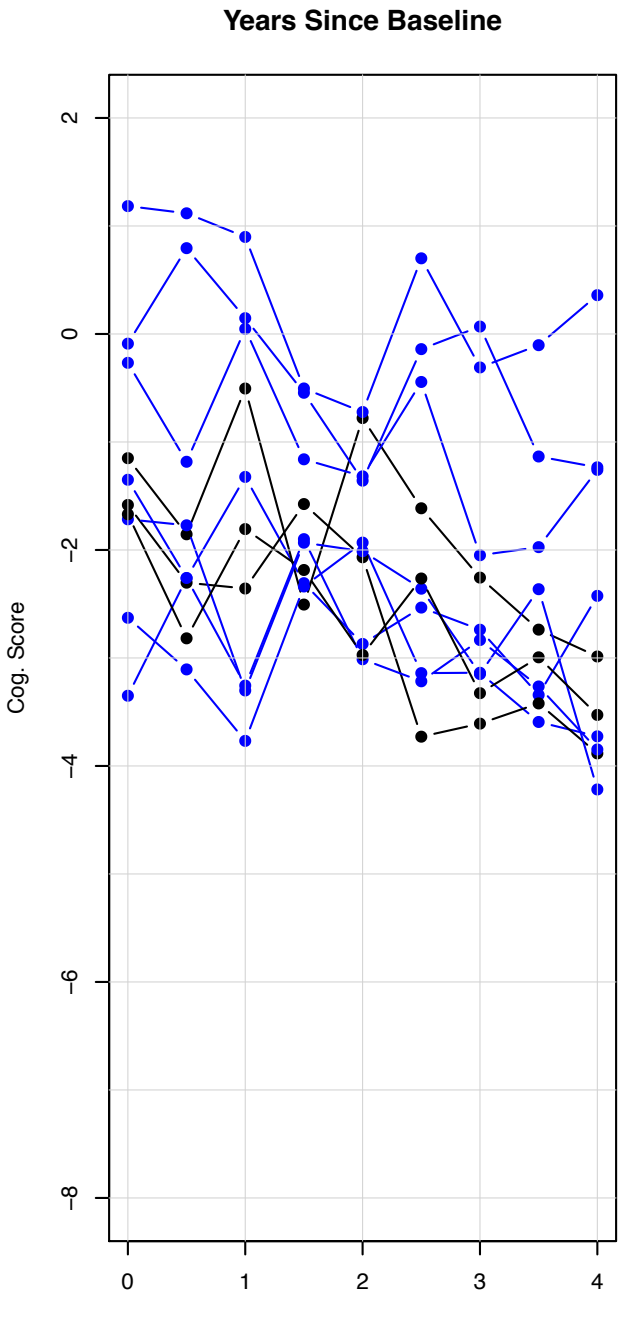

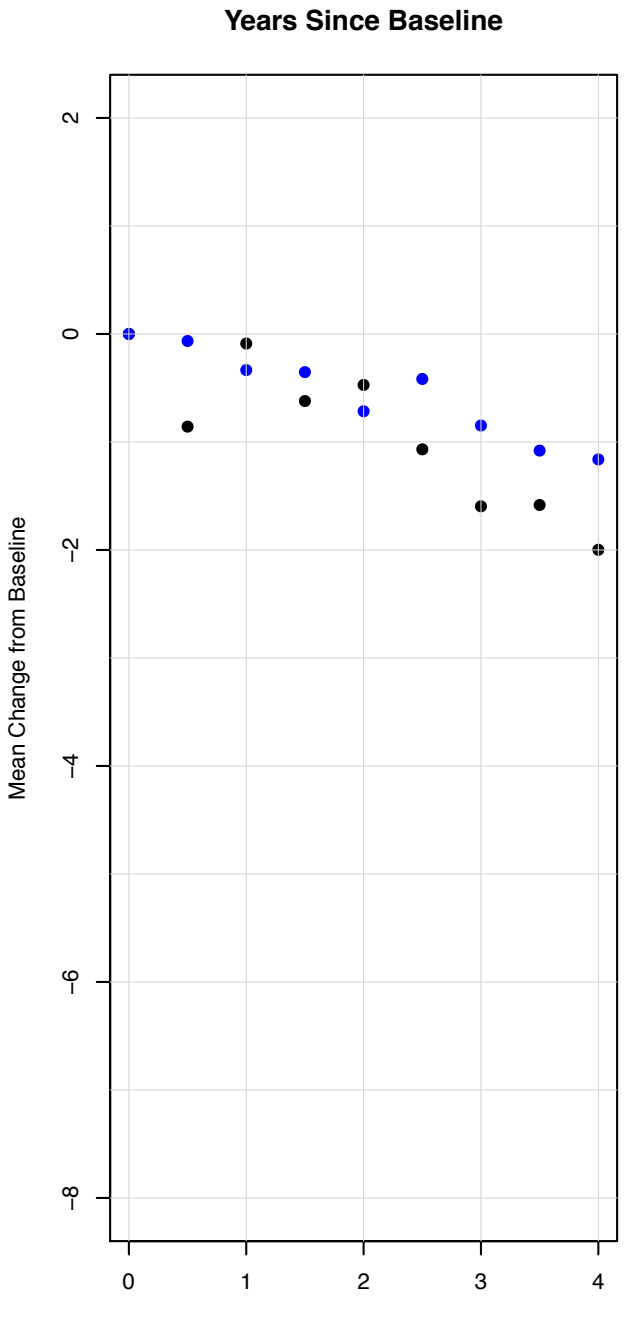

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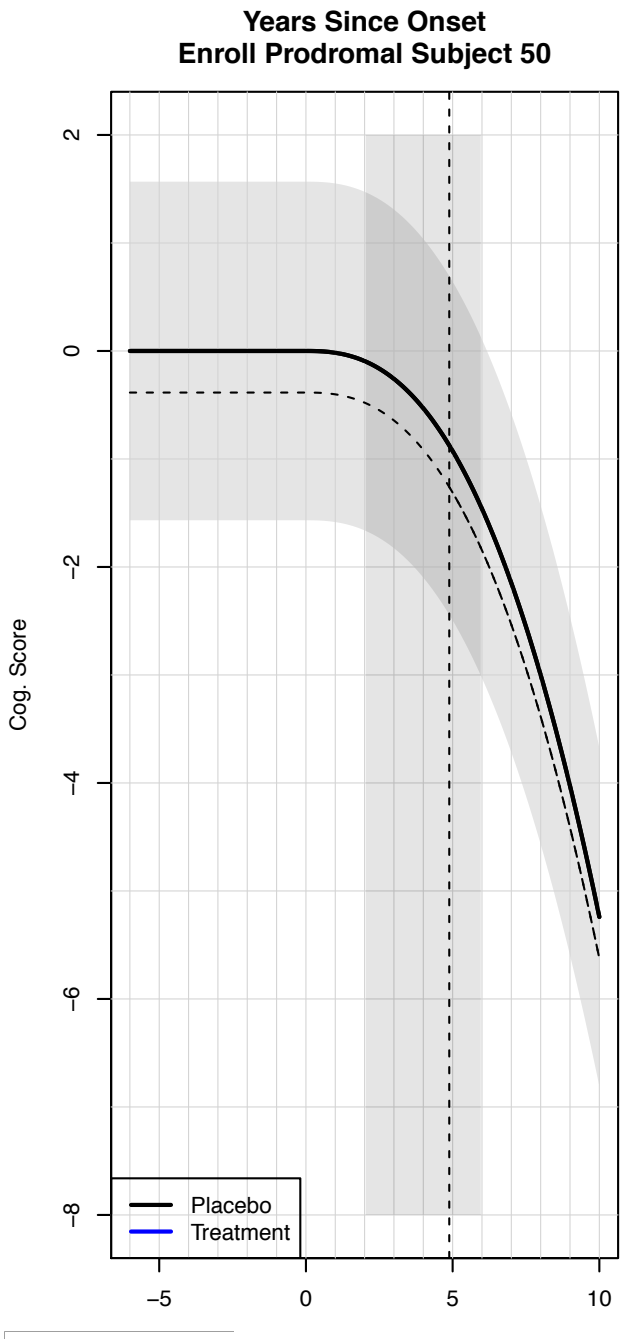

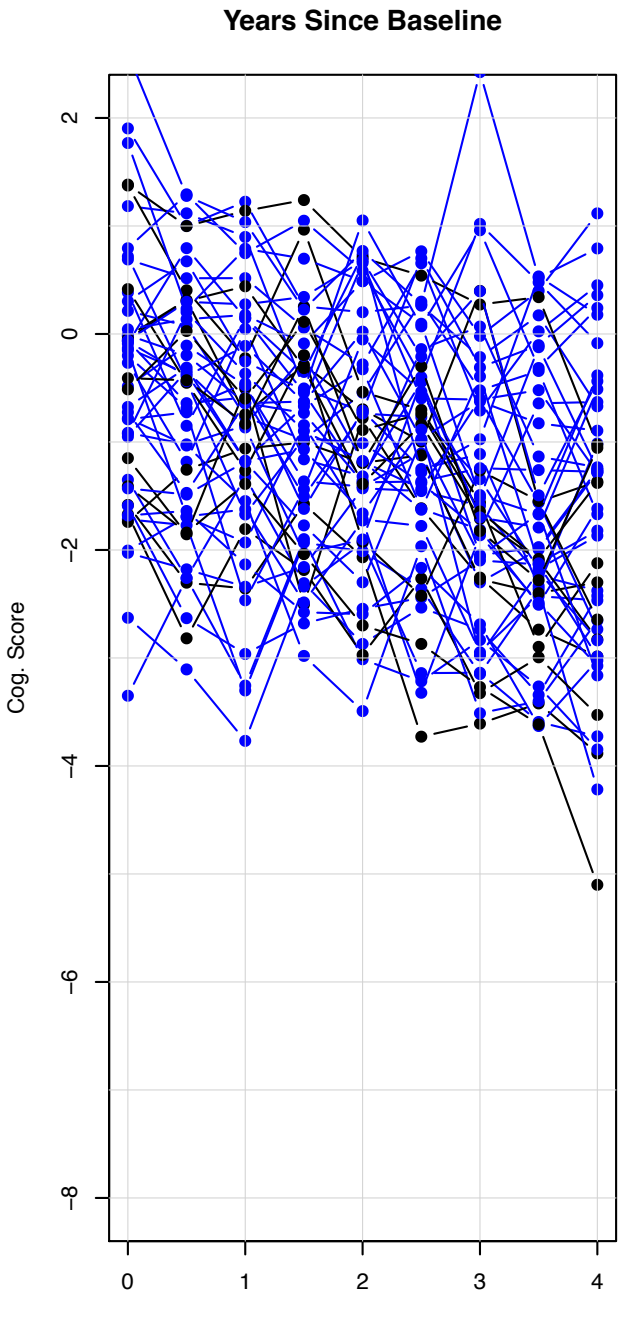

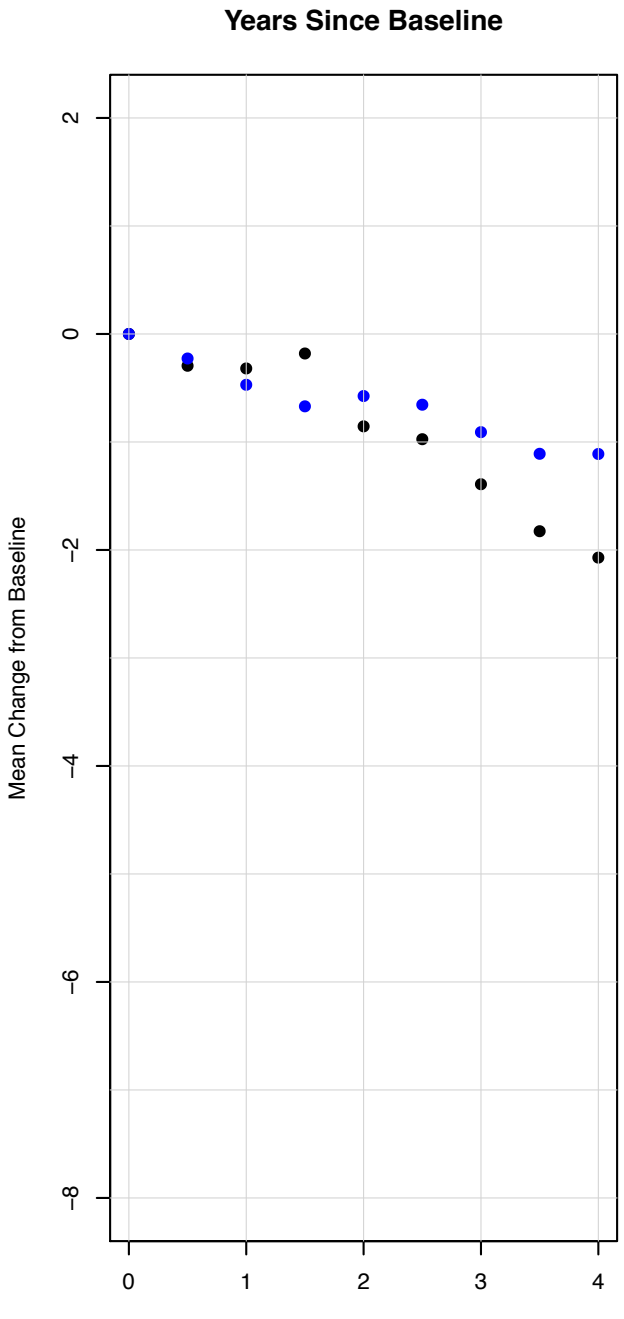

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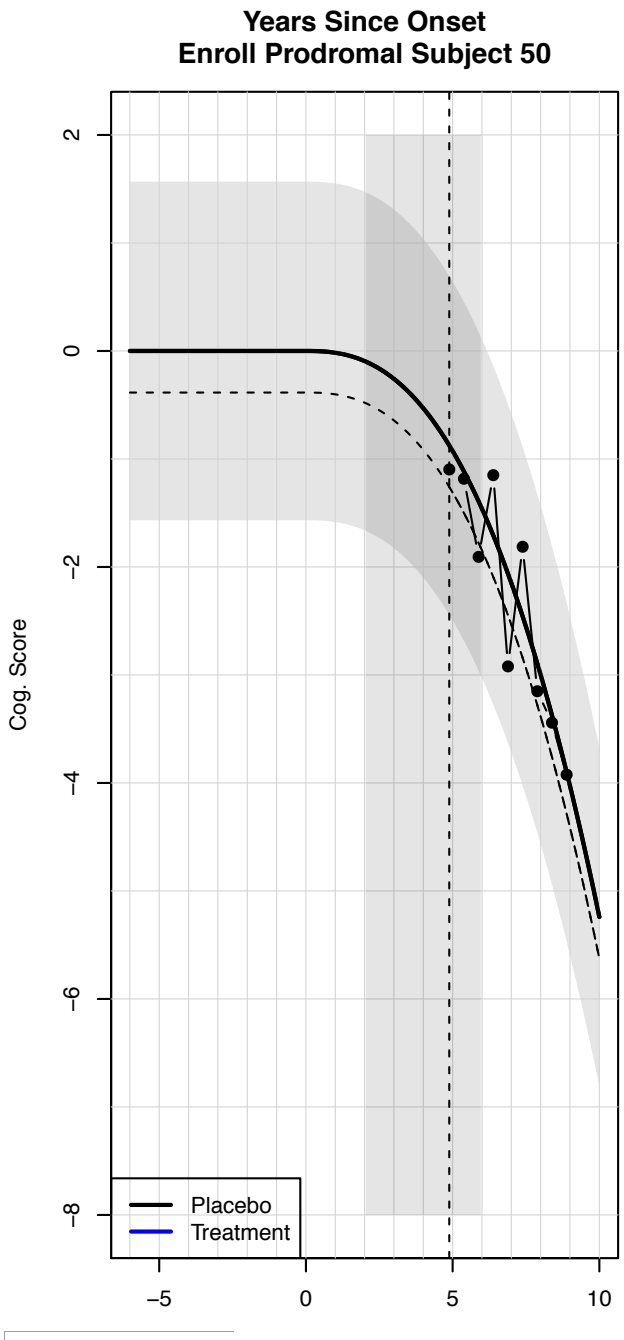

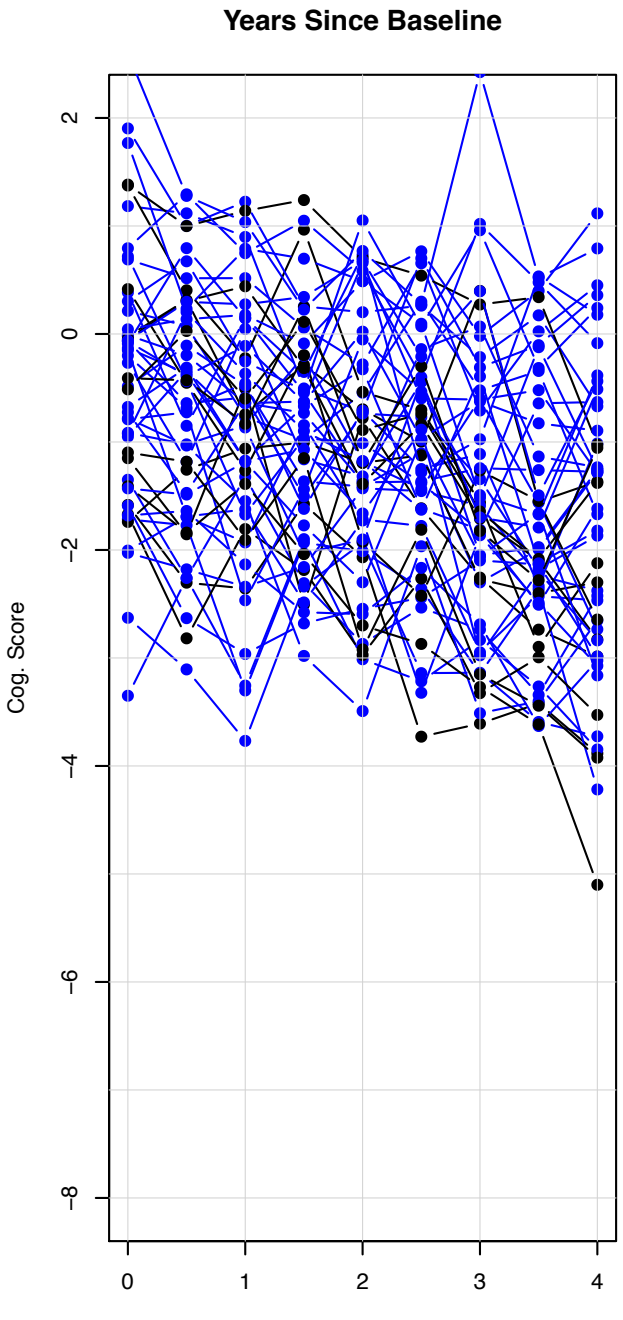

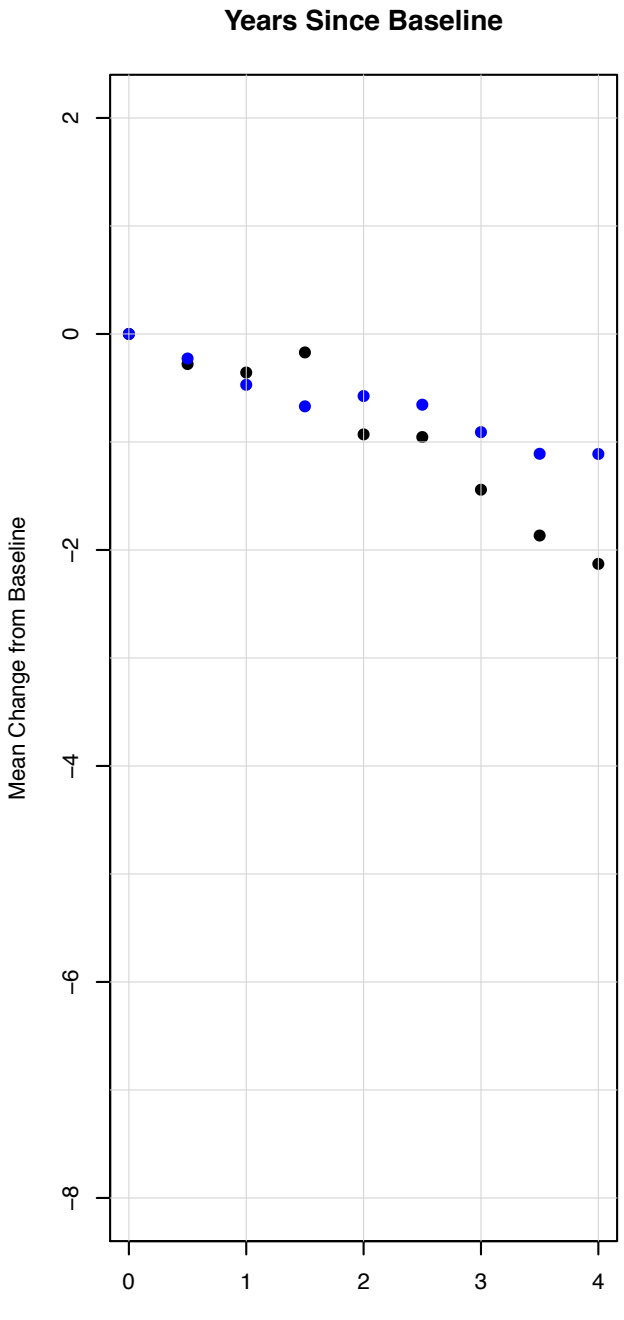

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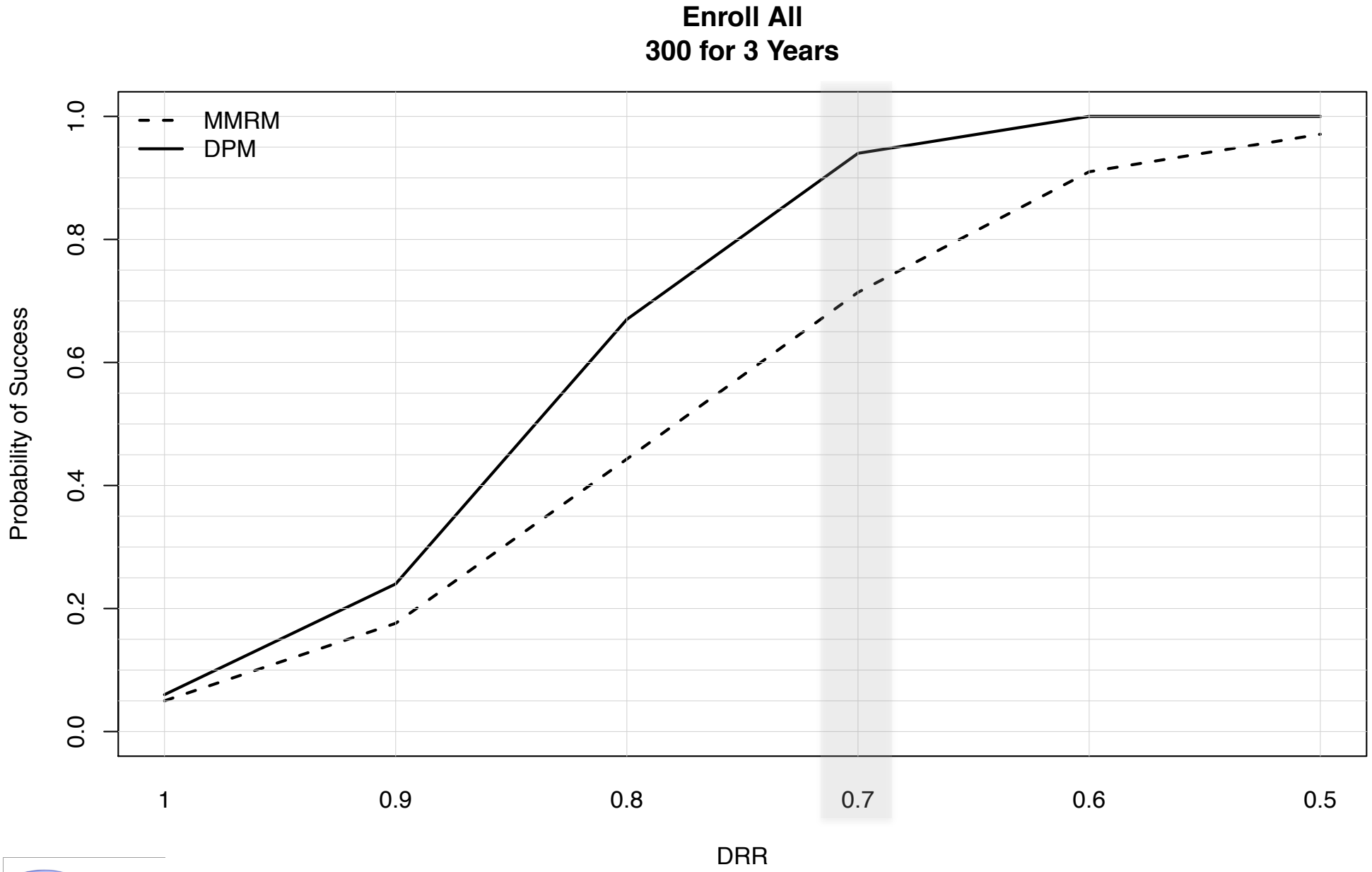
CLINICAL TRIAL SIMULATIONS

What benefit do we get from DPM compared to MMRM?



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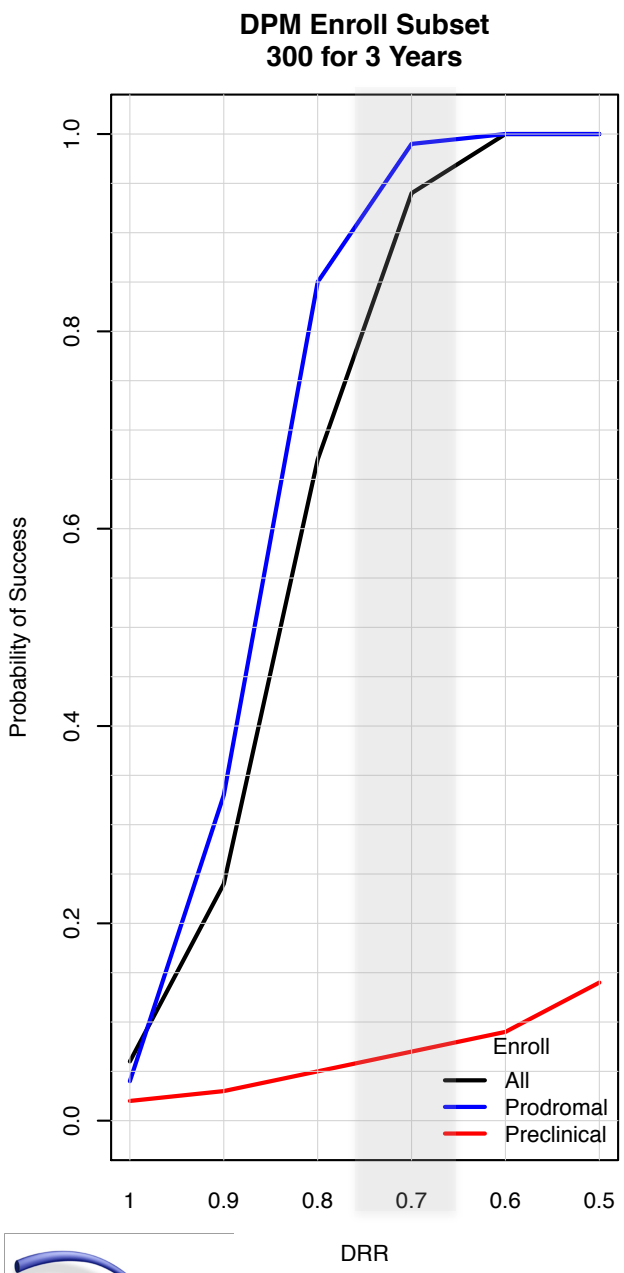
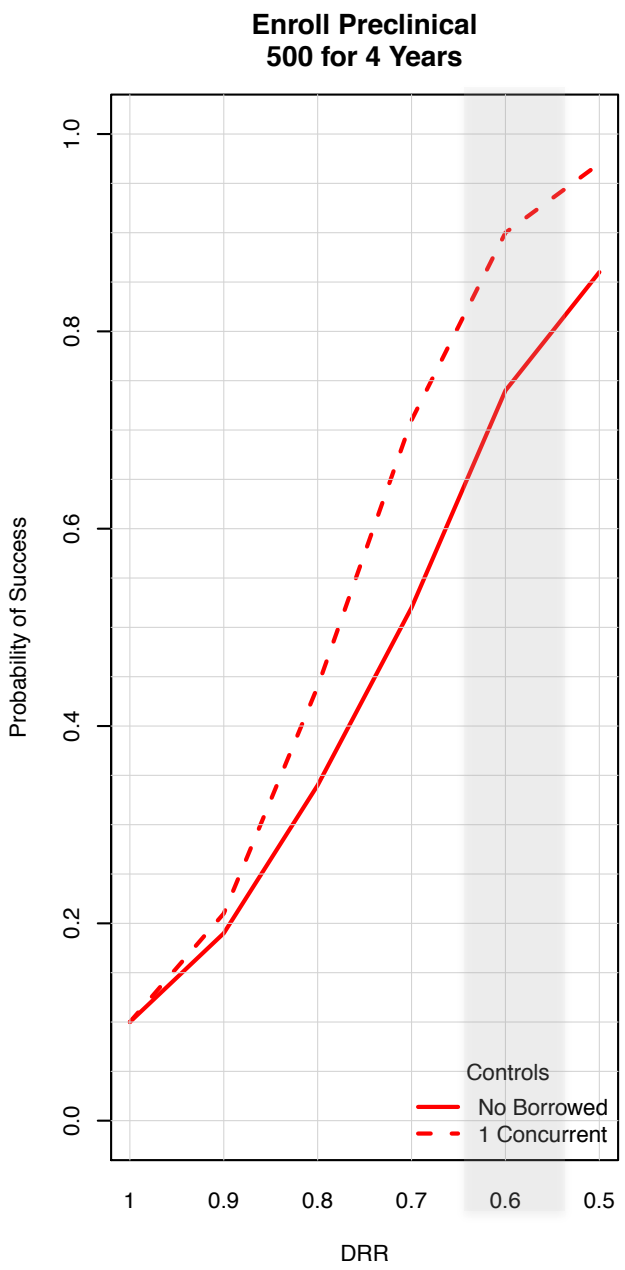
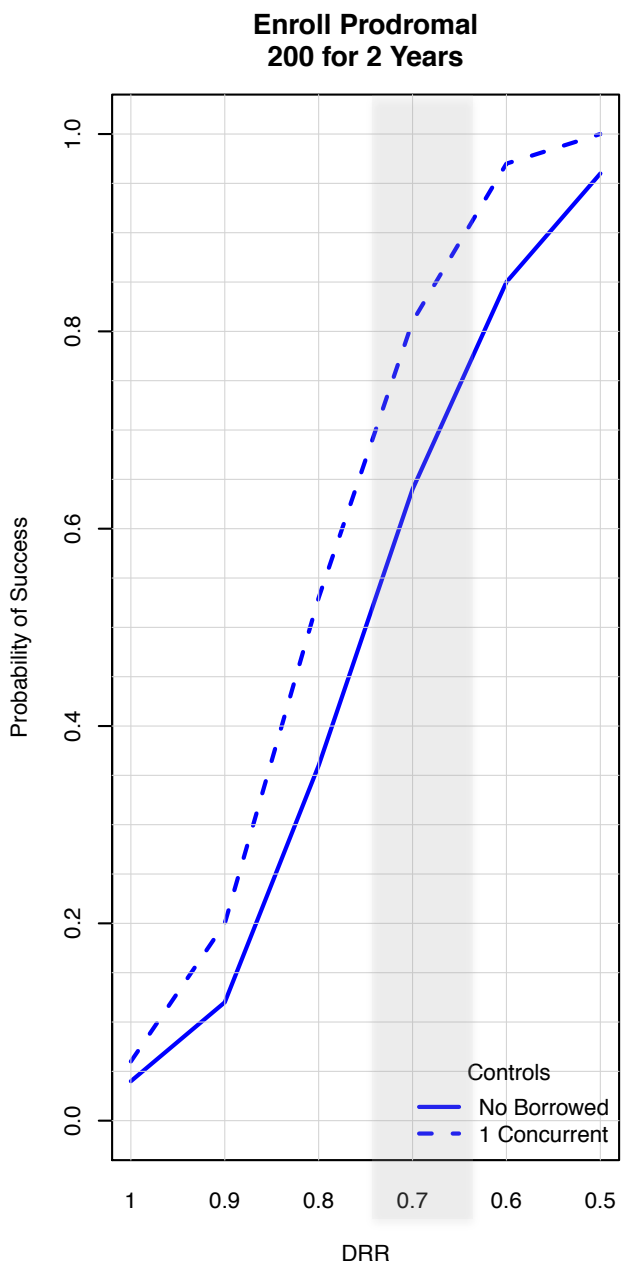
What if we only want to enroll a subset of the population?







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GNE MYOPATHY

Background: GNE Myopathy

- **GNE Myopathy**
  - Rare genetic muscle disease
  - Slowly progressive muscle weakness and atrophy
  - Estimated worldwide prevalence: 4-21/1,000,000
  - No known treatment available
- **Develop trial designs that can study and confirm effectiveness of novel therapies**
  - *Lack of well-suited primary endpoints: different muscles involved at different stages of disease*

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Aug 22, 2017

Ultragenyx Announces Top-Line Results from Phase 3 Study of Ace-ER in GNE Myopathy

Study did not meet its primary endpoint

NOVATO, Calif., Aug. 22, 2017 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ:RARE), a biopharmaceutical company focused on the development of novel products for rare and ultra-rare diseases, today announced that a Phase 3 study evaluating aceneuramic acid extended release (Ace-ER) in patients with GNE Myopathy (GNEM) did not achieve its primary endpoint of demonstrating a statistically significant difference in the upper extremity muscle strength composite score compared to placebo. The study also did not meet its key secondary endpoints. Adverse events were generally balanced between Ace-ER and placebo and safety was consistent with previously released Ace-ER data. Ultragenyx plans to discontinue further clinical development of Ace-ER.

"We are disappointed by these results, as we had hoped that Ace-ER would offer a new option for GNEM patients. We would like to thank the patients, caregivers, and investigators involved in the Ace-ER development program," said Emil D. Kakkis, M.D., Ph.D., Chief Executive Officer and President of Ultragenyx. "This outcome does not affect our overall strategy, as the company moves forward with multiple preclinical and clinical programs and regulatory filings."

The Phase 3 Ace-ER study enrolled 89 adults with GNEM able to walk $\geq$ 200 meters in the six minute walk test. Patients were randomized 1:1 to Ace-ER at a dose of 6g/day or placebo for 48 weeks. The study did not meet the primary endpoint of demonstrating a statistically significant improvement in UEC score (+0.74 kg, p=0.5387) for Ace-ER treated patients (n=45, -2.25 kg) compared to placebo (n=43, -2.99 kg) patients for the change from baseline to 48 weeks. There were three pre-specified key secondary endpoints, including the lower extremity muscle strength composite score as measured by hand-held dynamometry (HHD), physical functioning using the Mobility domain of the GNE Myopathy-functional activity scale (GNEM-FAS), and a measure of muscle strength in knee extensors. The study did not meet any of these key secondary endpoints.

Natural History Data

- **Sample Size:** 38 Patients
- **Visits:** Every 3-6 months
  - Number of months from baseline per patient ranges from 0-32
- **Possible Primary Endpoints:**
  - 10-point muscle score on Quantitative Muscle Assessment (QMA) for multiple muscle groups
    - Available predicted muscle score for person of the same age, gender and BMI
    - Report proportion muscle score relative to predicted score

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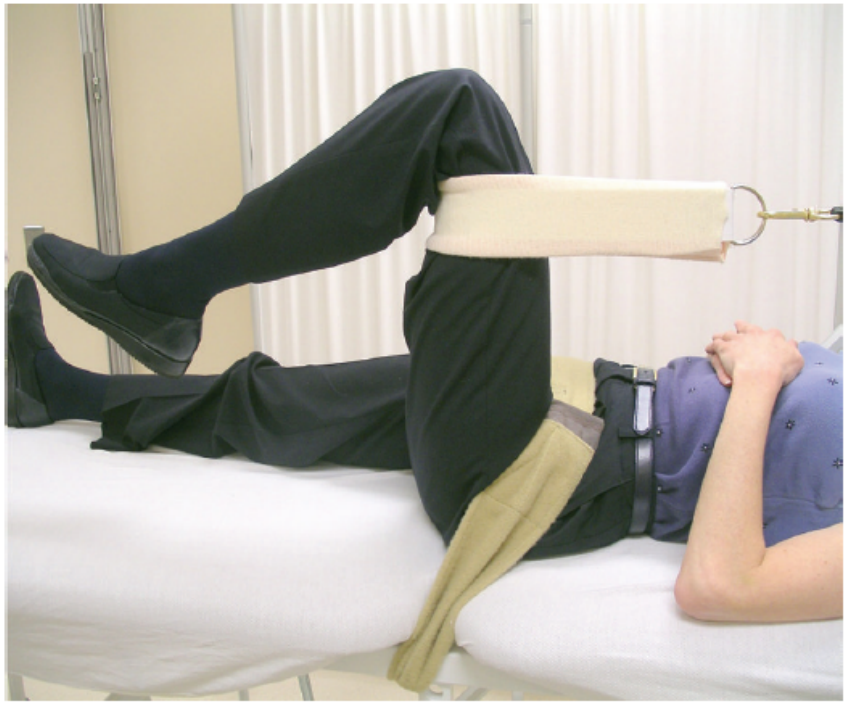
Quantitative Muscle Assessment (QMA)

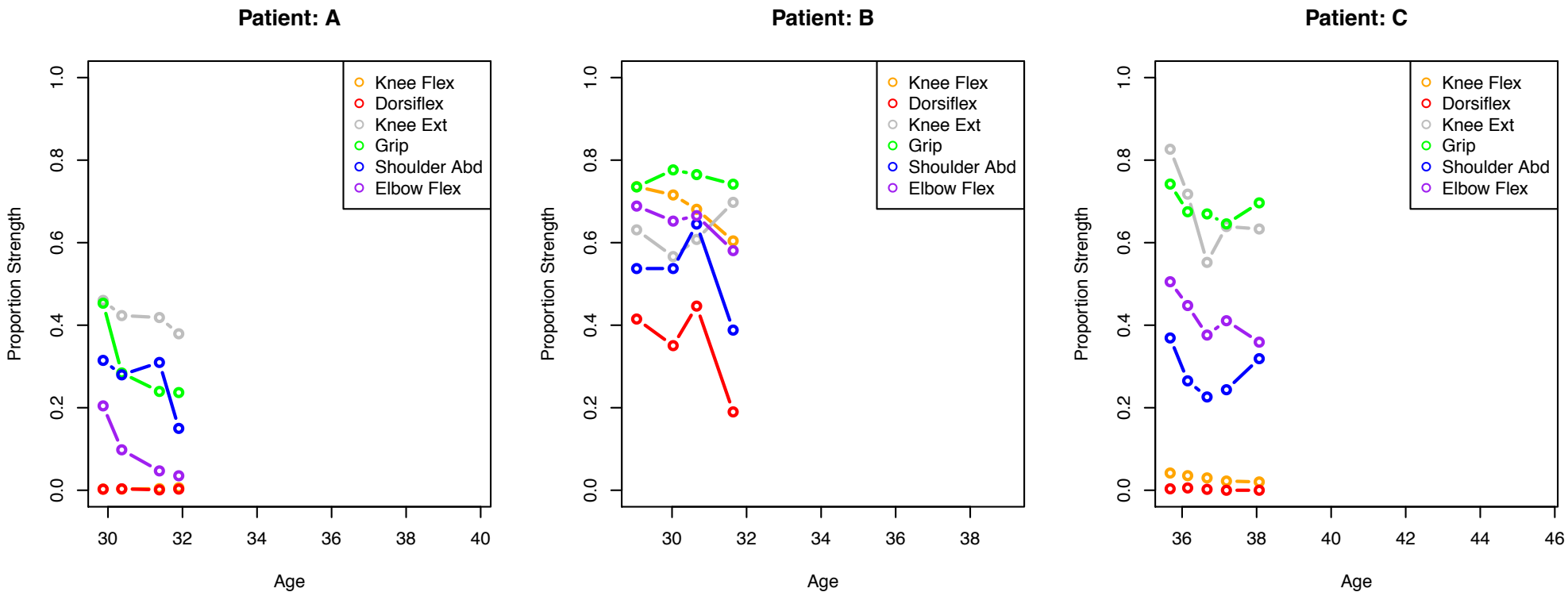


Harris-Love et al, Rehab Research Practice, 2014

	Muscle Group	Measured Strength (kg)	Percent Predicted*
Upper Extremities	L Grip	39.46	83.11%
	R Grip	45.93	91.41%
	L Wrist Ext	11.97	80.15%
	R Wrist Ext	16.91	105.91%
	L Shoulder Abd	21.50	88.53%
	R Shoulder Abd	20.24	73.22%
	L Elbow Flex	20.60	71.11%
	R Elbow Flex	22.64	69.08%
	L Elbow Ext	10.72	47.54%
	R Elbow Ext	11.89	51.20%
	Sum Upper	*221.84*	*77.02%*
Lower Extremities	L Dorsiflex	8.02	25.83%
	R Dorsiflex	7.42	23.98%
	L Hip Abd	27.48	77.38%
	R Hip Abd	31.27	90.44%
	L Hip Ext	56.40	117.54%
	R Hip Ext	54.28	114.39%
	L Knee Ext	31.49	53.07%
	R Knee Ext	39.02	64.09%
	L Knee Flex	23.35	81.94%
	R Knee Flex	22.13	74.91%
	Sum Lower	*300.83*	*74.15%*
	Sum Strength	522.66	75.34%

* Based on age, gender and BMI

Natural History Data



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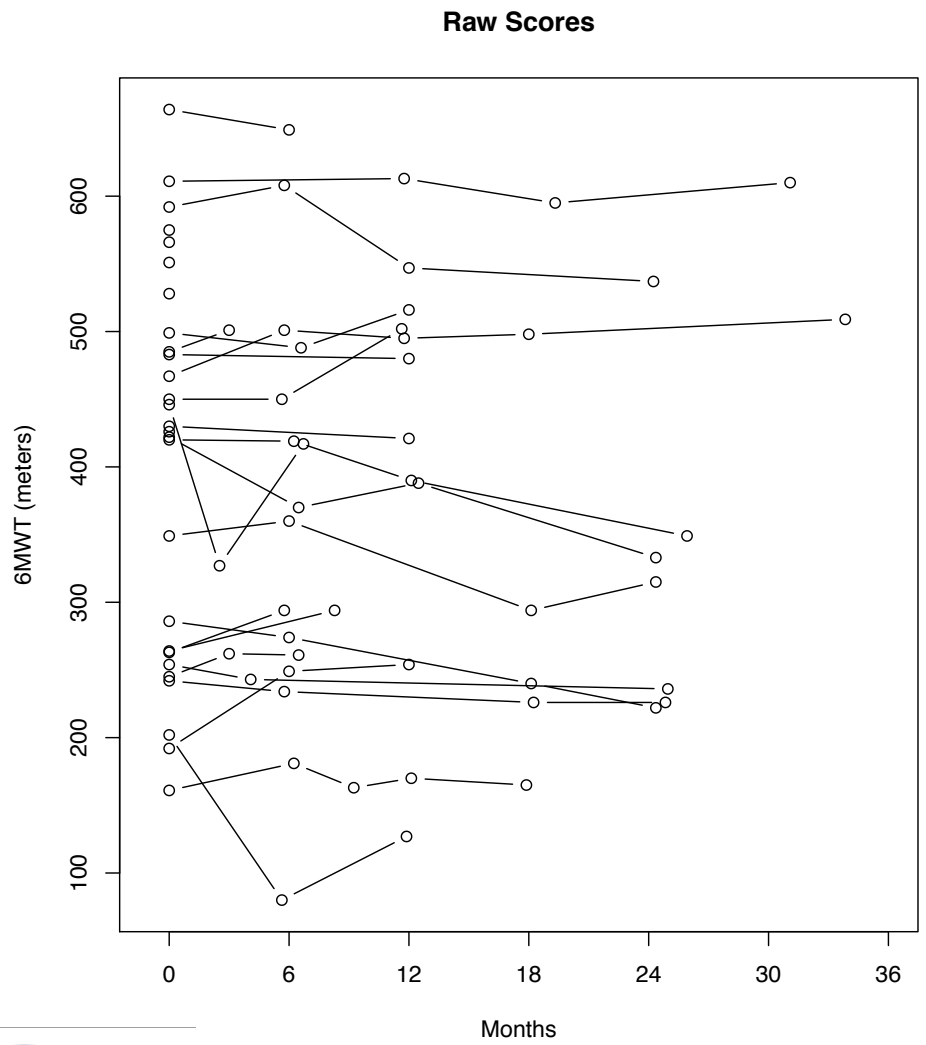
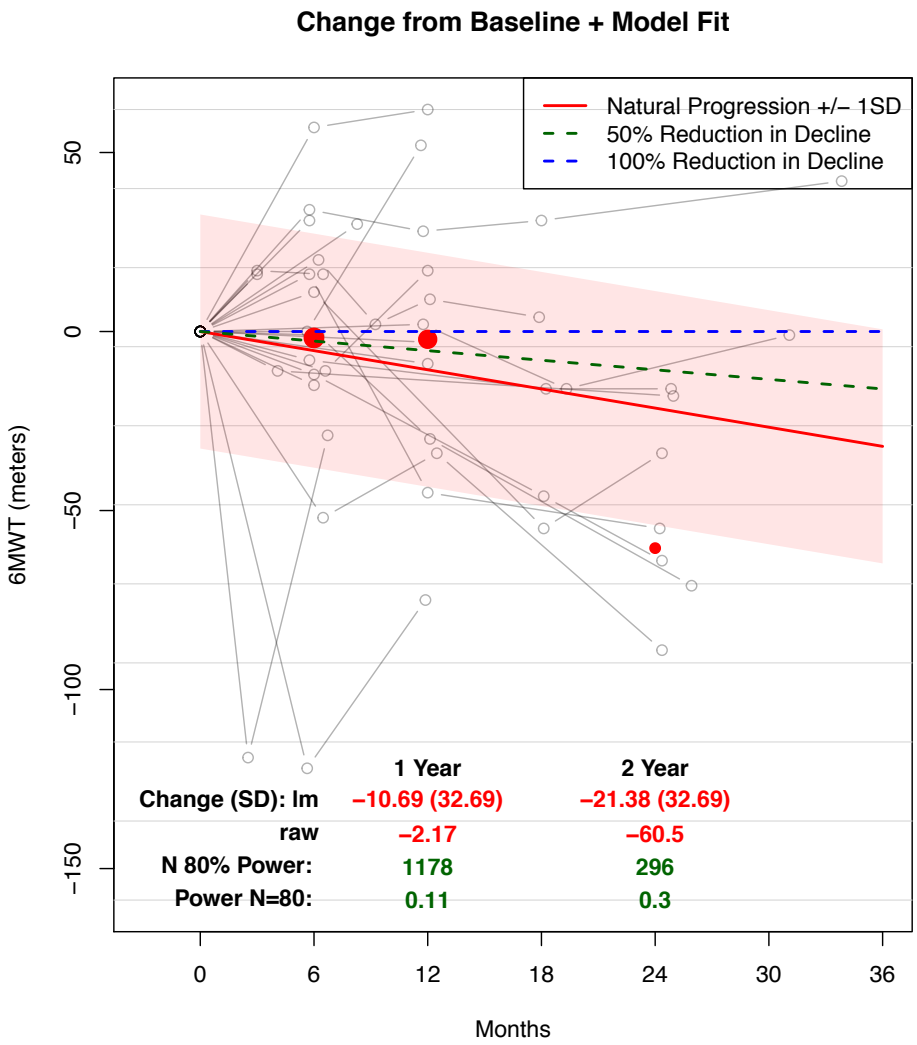
Possible Primary Endpoints: 6 Min. Walk





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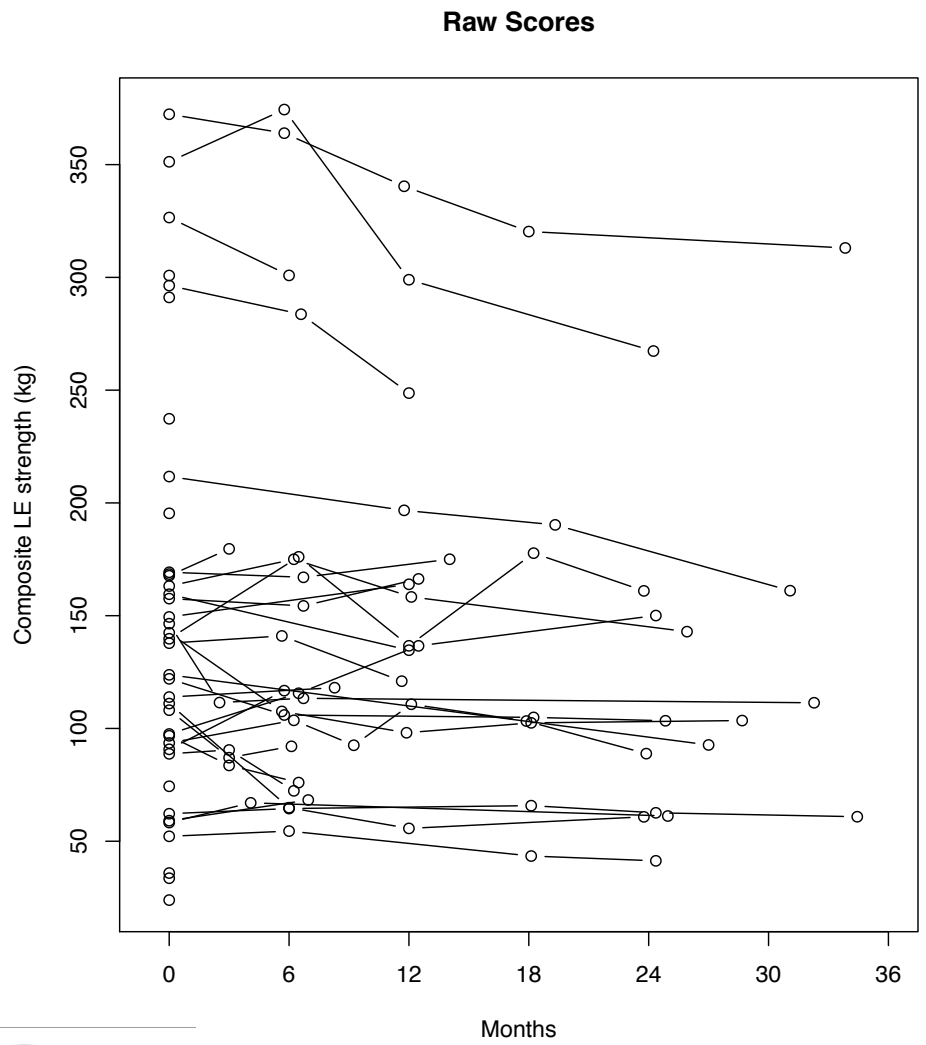
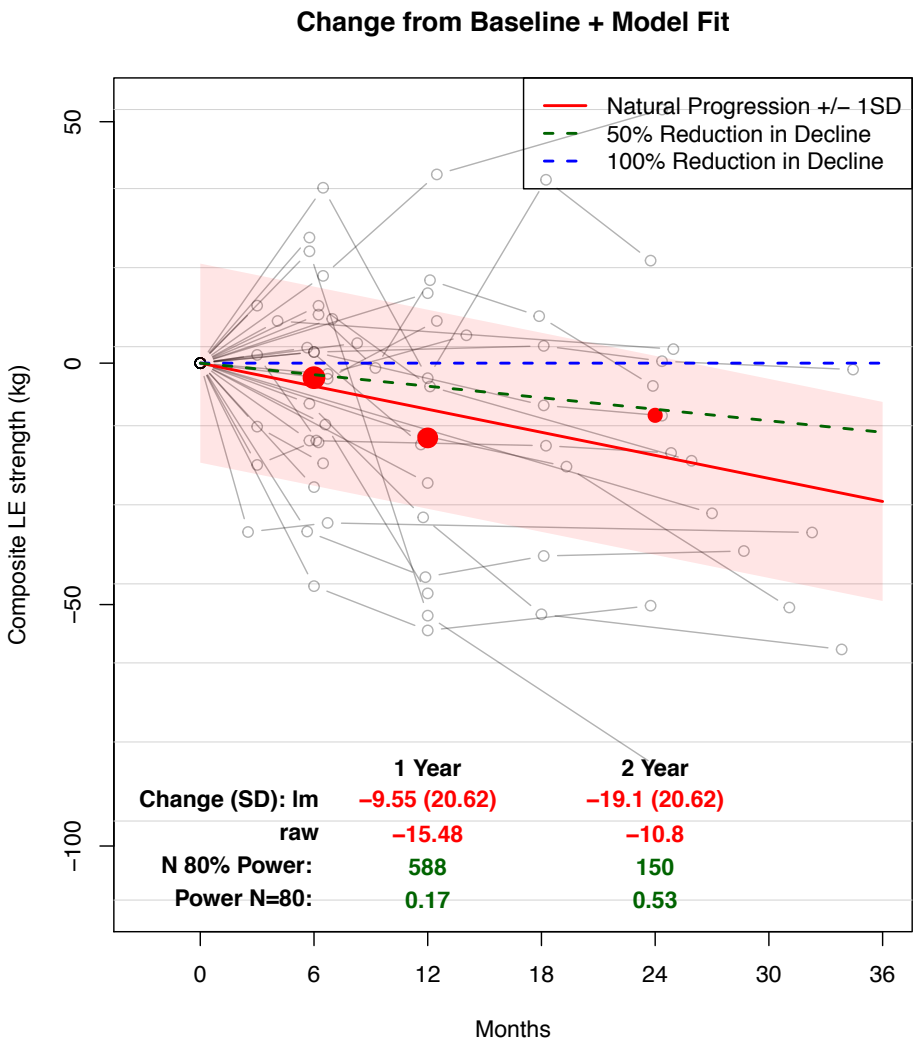
Possible Primary Endpoints: Lower Extremity Composite





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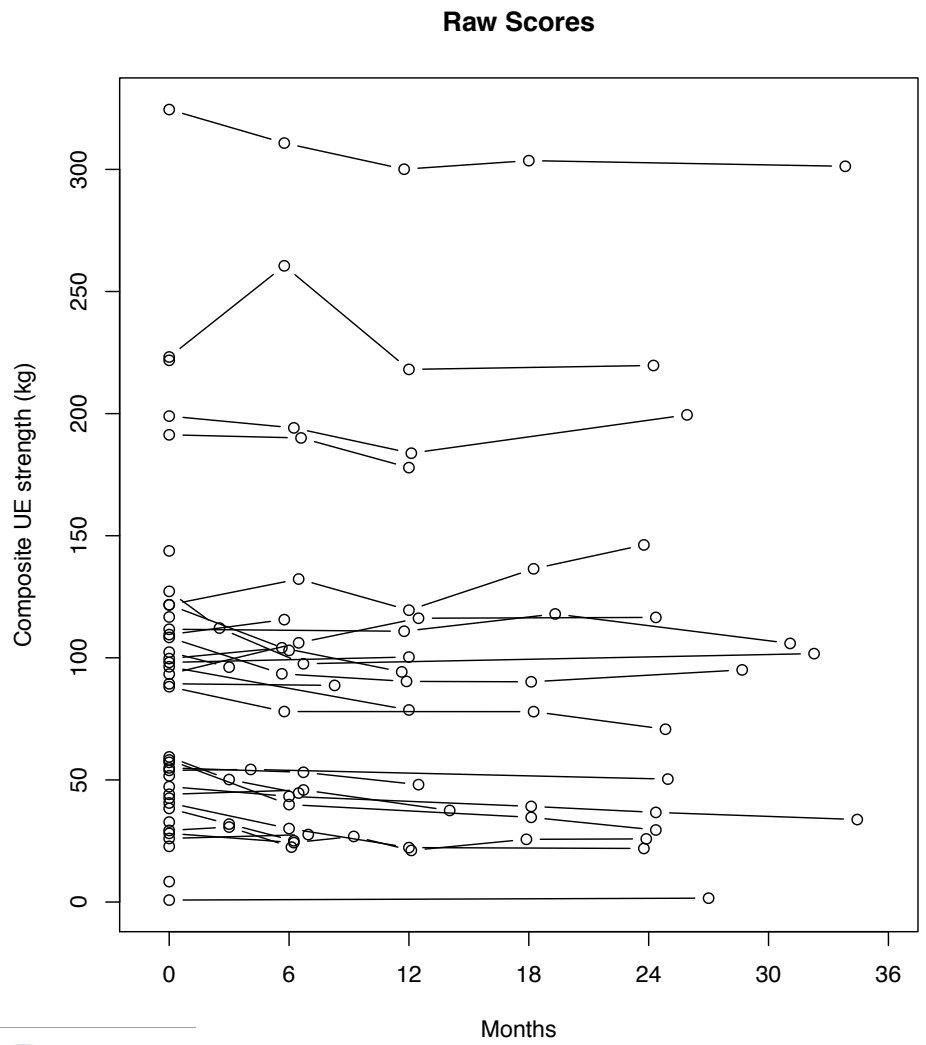
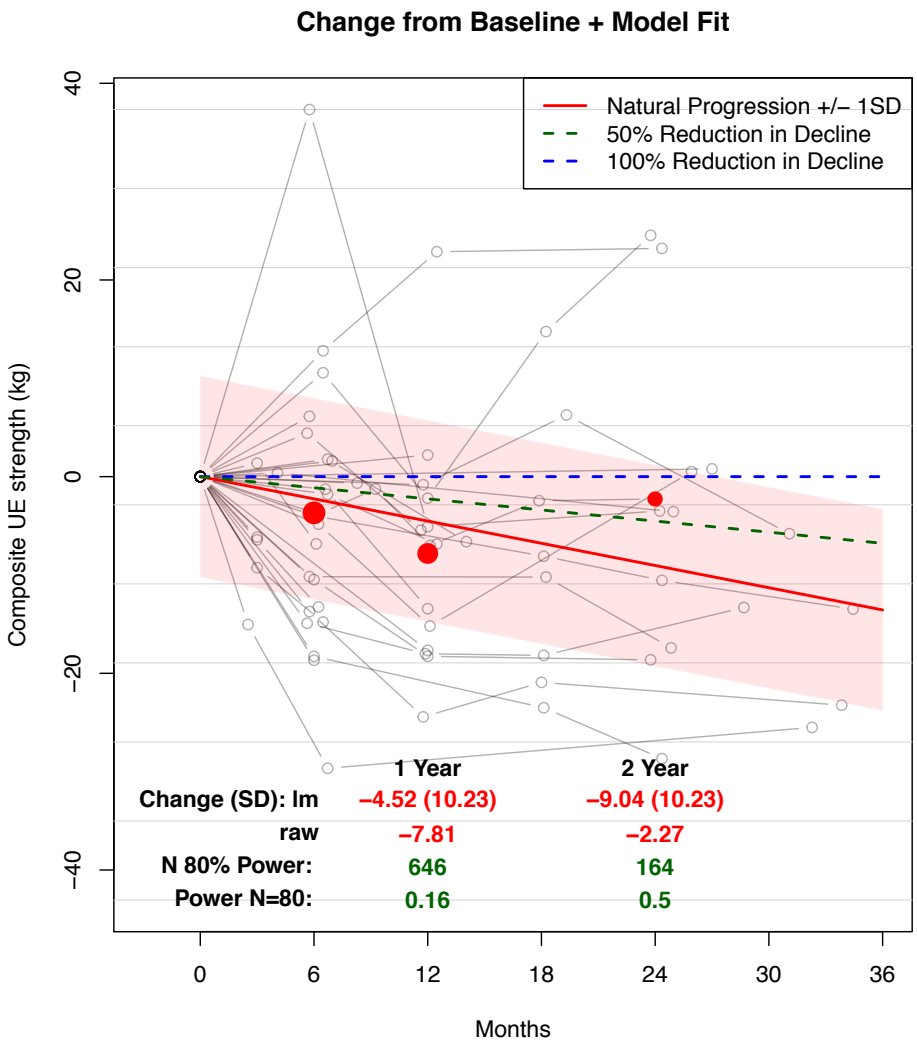
Possible Primary Endpoints: Upper Extremity Composite





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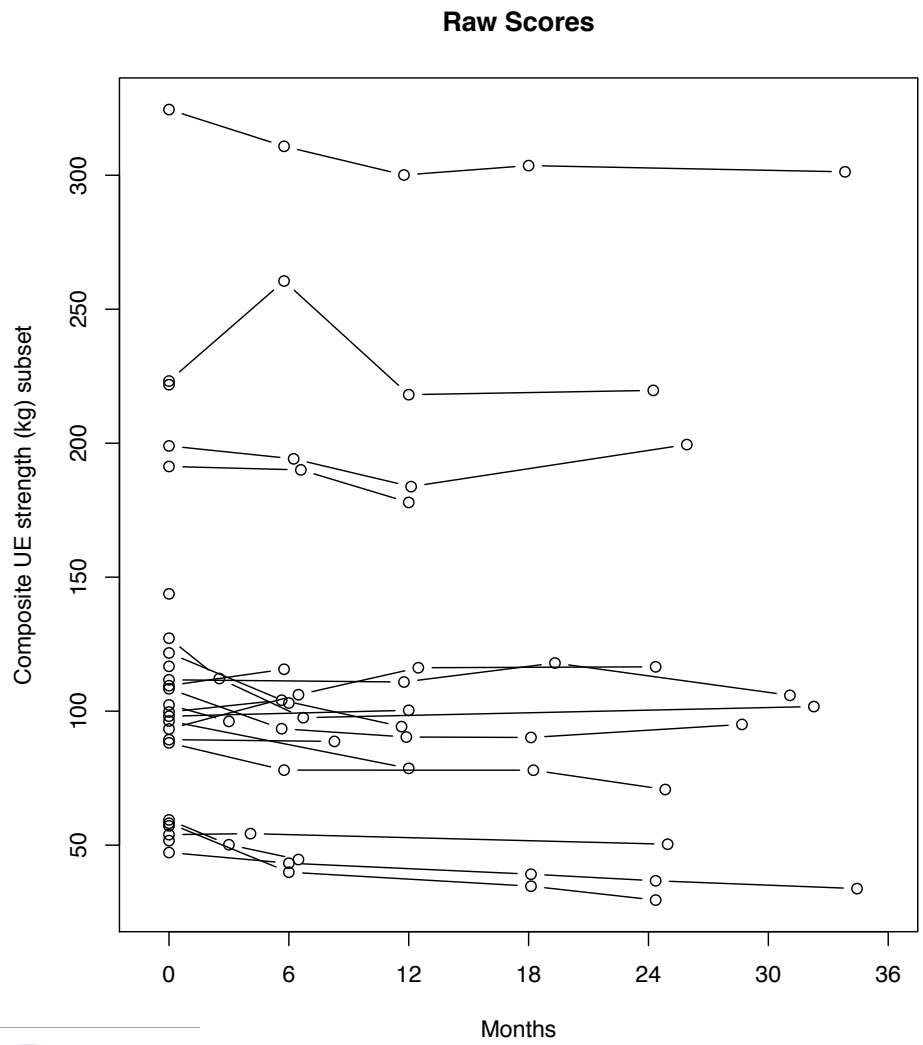
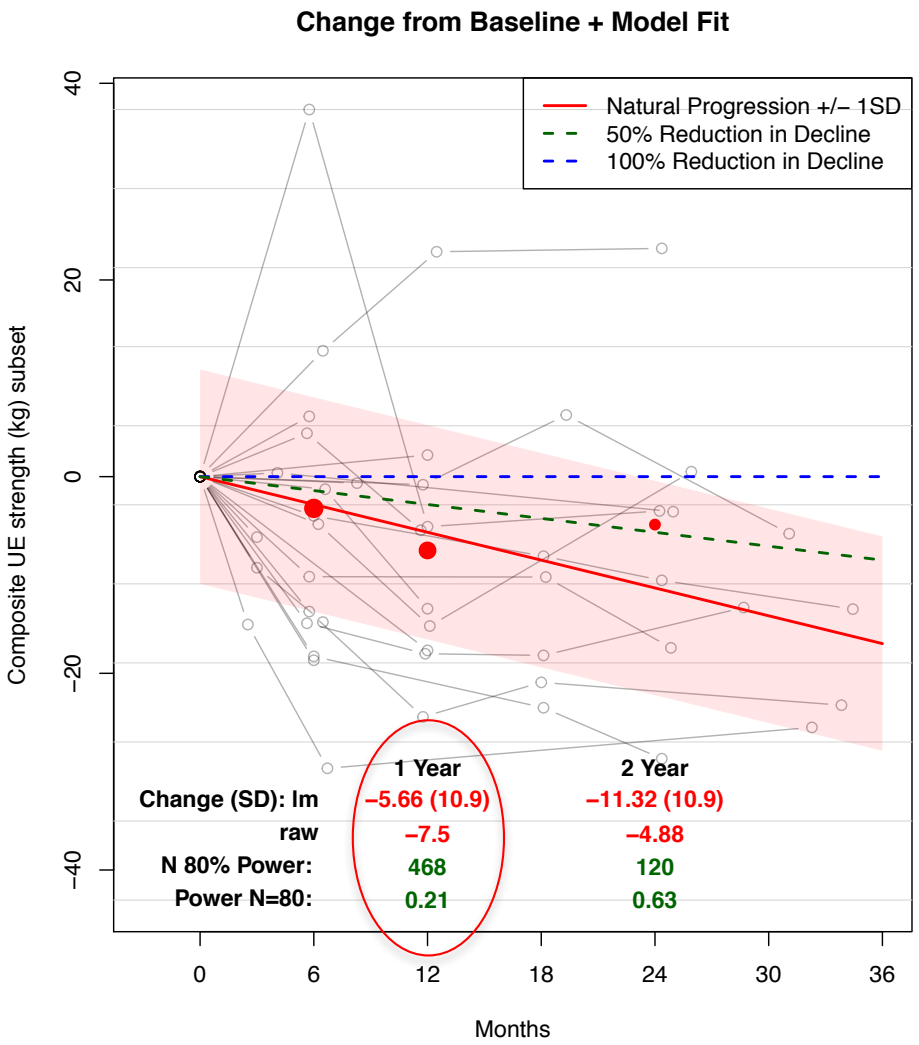
Possible Primary Endpoints: Upper Extremity Composite Subset*





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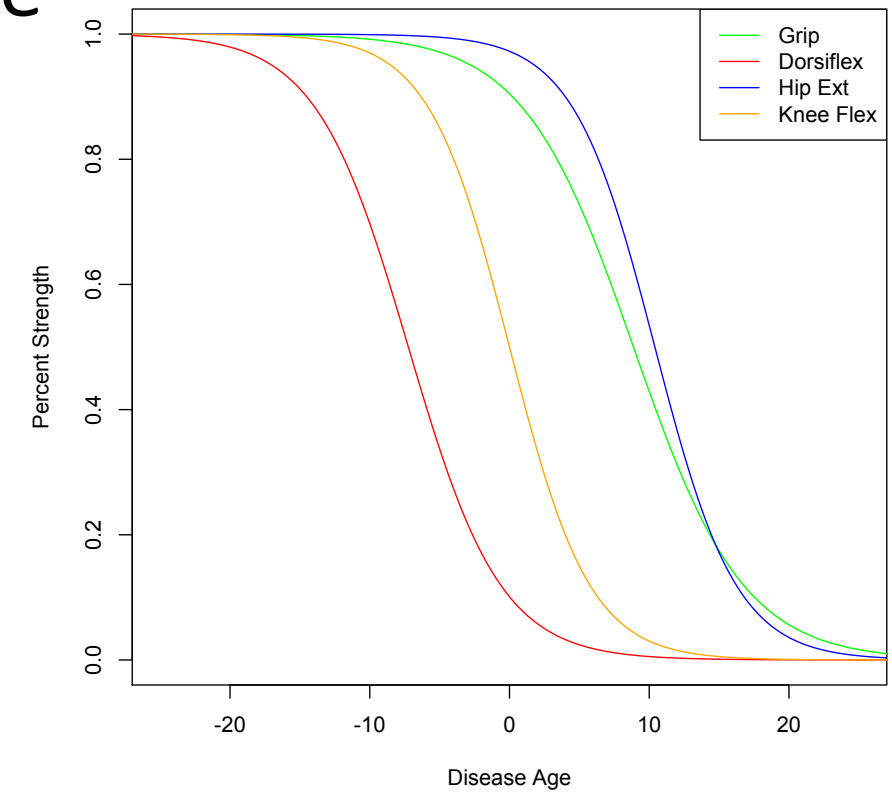
JOINT MODEL OF NATURAL PROGRESSION

Model Muscle Decay

- **Goal:** Model the expected decay of each muscle over time



* Need to align patients based on an unknown “disease age”

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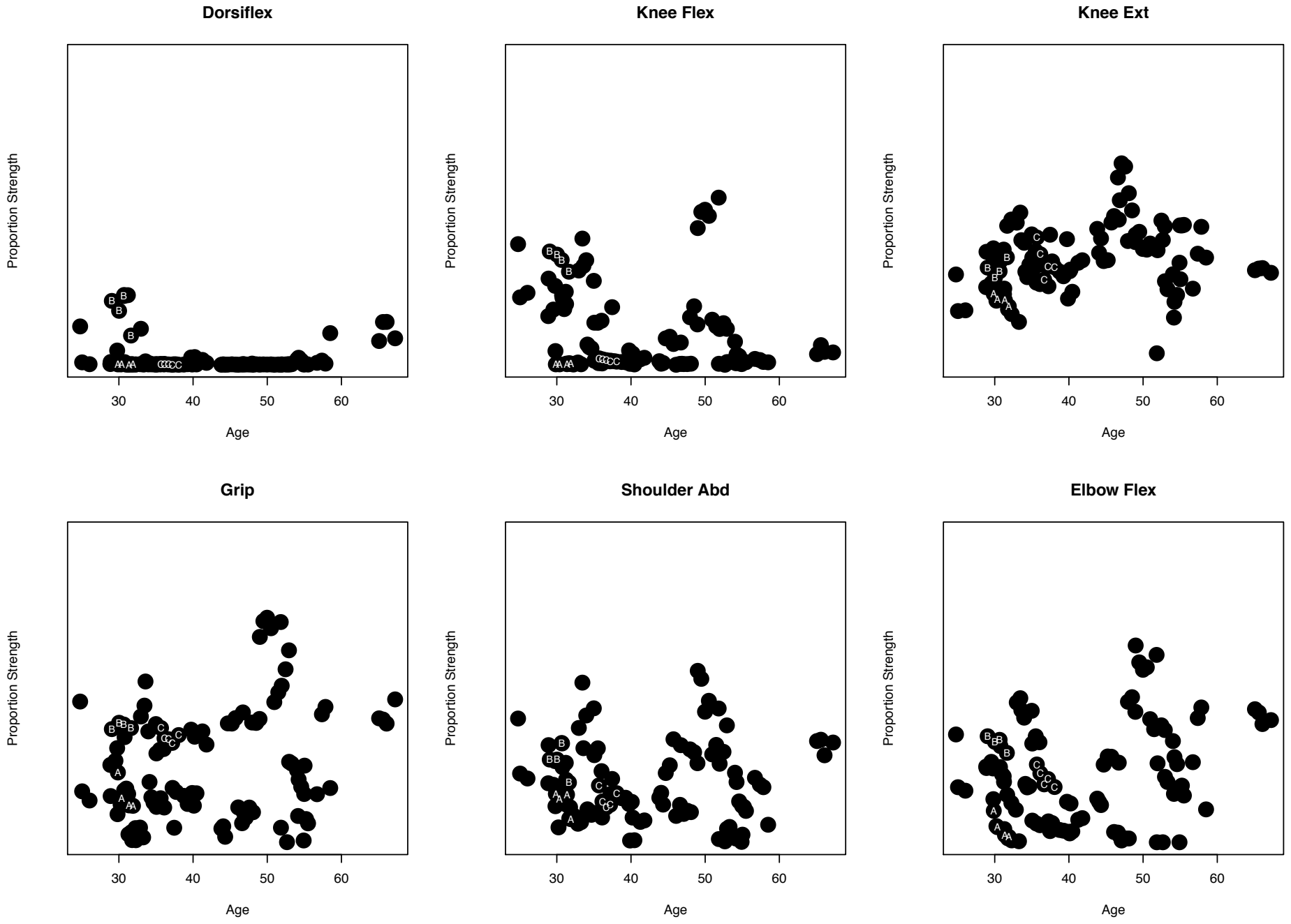
Decline vs. Age



Decline vs. Knee Flex Disease Age

- Fit a decay model to proportion muscle strength in knee flex
- Determine disease age by aligning patients to best fit knee flex decay model
  - Define disease age to be zero when knee flex is 50% of max muscle strength
- What does the proportion strength in the other muscle groups look like based on this disease age?

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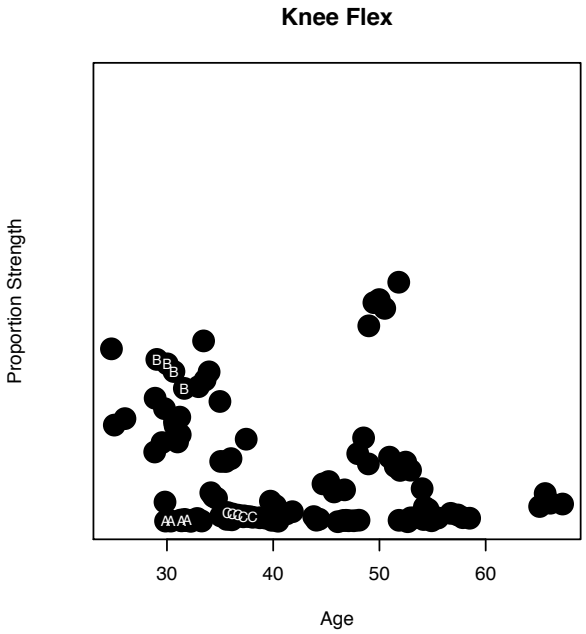
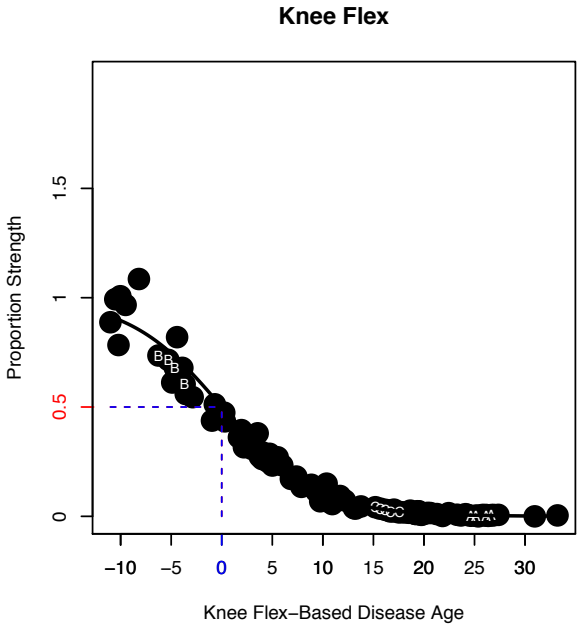
Decline vs. Knee Flex Disease Age

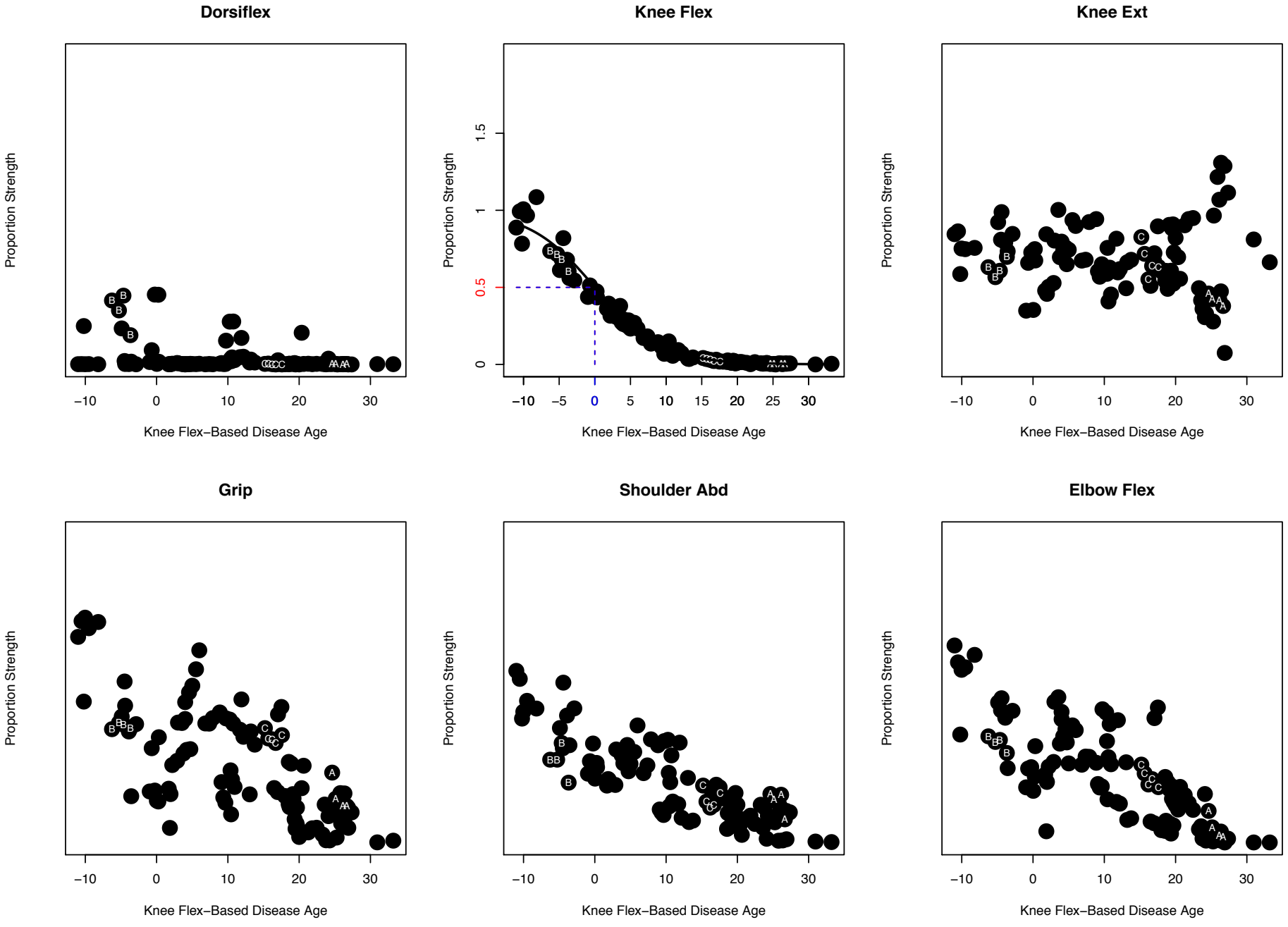




Summary:

- Patient B stronger on Knee Flex than most individuals
- Patient B (28 years old) have a Knee Flex-based disease age much less than patient A (30 years old)

Decline vs. Knee Flex Disease Age



Decline vs. Joint Disease Age

$$Y_{i,j,k} \sim N(\mu_{i,j,k}, (\sigma_k \mu_{i,j,k})^2 + \delta)$$

$$\mu_{i,j,k} = \text{logit}^{(-1)}[\theta_k + \beta_k (t_{i,j} - \alpha_i)] * M_{i,k}$$

- Model proportion of muscle strength
  - normal distribution
  - variance is a function of mean and muscle-specific component
- Model mean based on logit decay function with components:
  - muscle specific location parameter (when the muscle begins to decay)
  - muscle specific slope parameter (rate of decay)
  - Subject-specific age adjustment parameter, determines "disease age"
  - Subject and muscle specific relative maximum, to account for variation in overall strength of the individual

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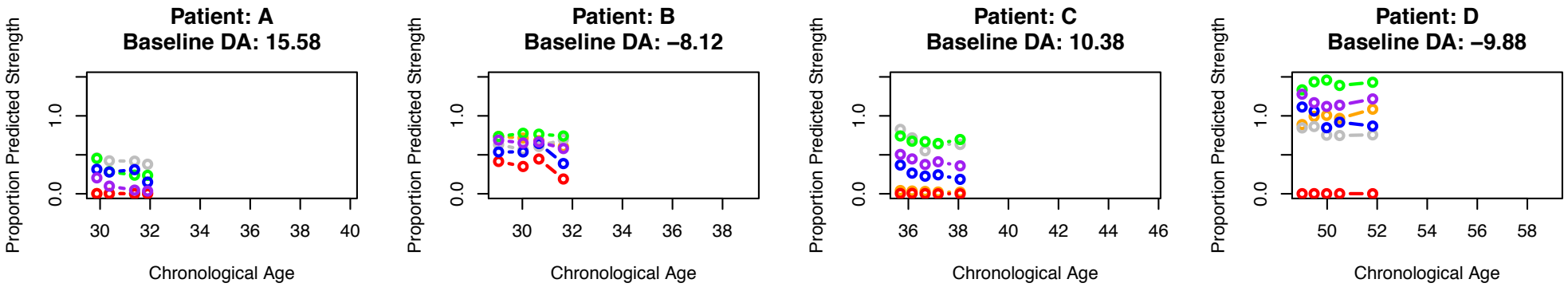
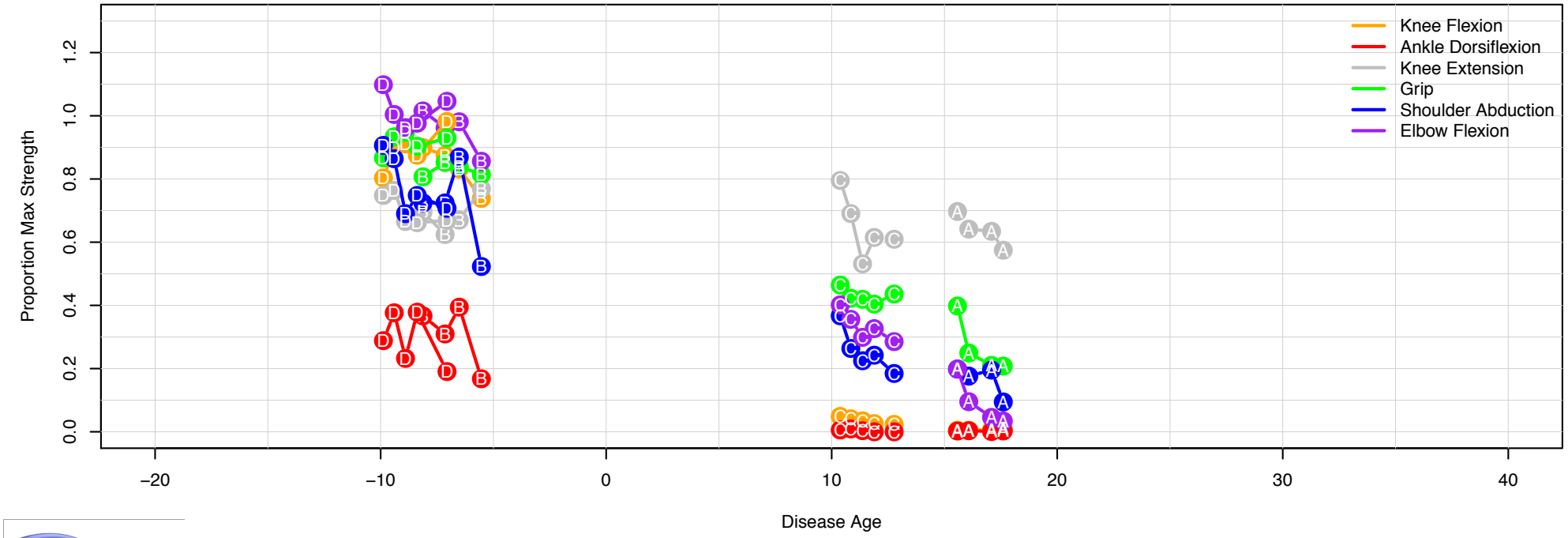
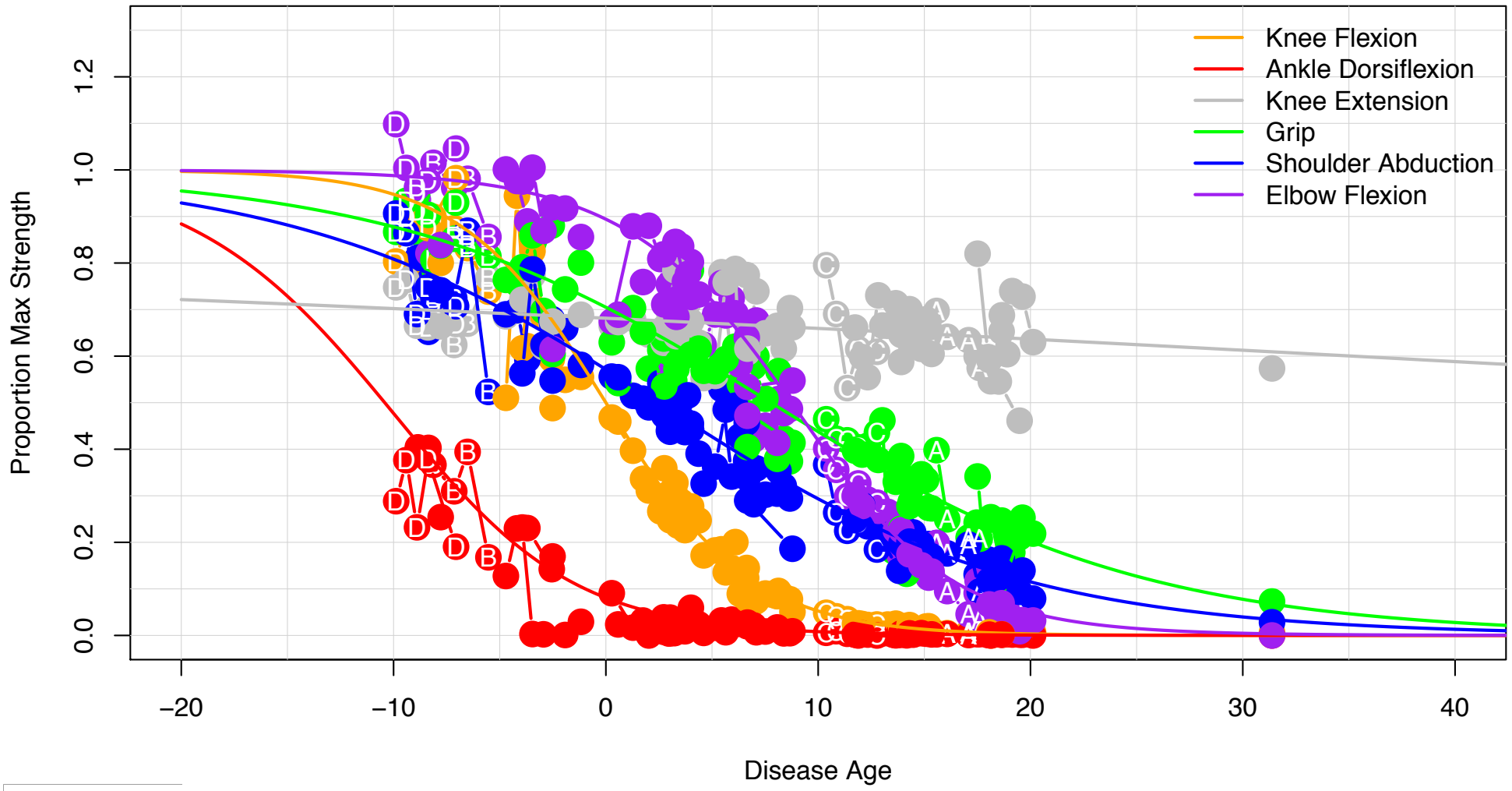
Disease Age Per Subject





Expected Muscle Decline vs. Disease Age



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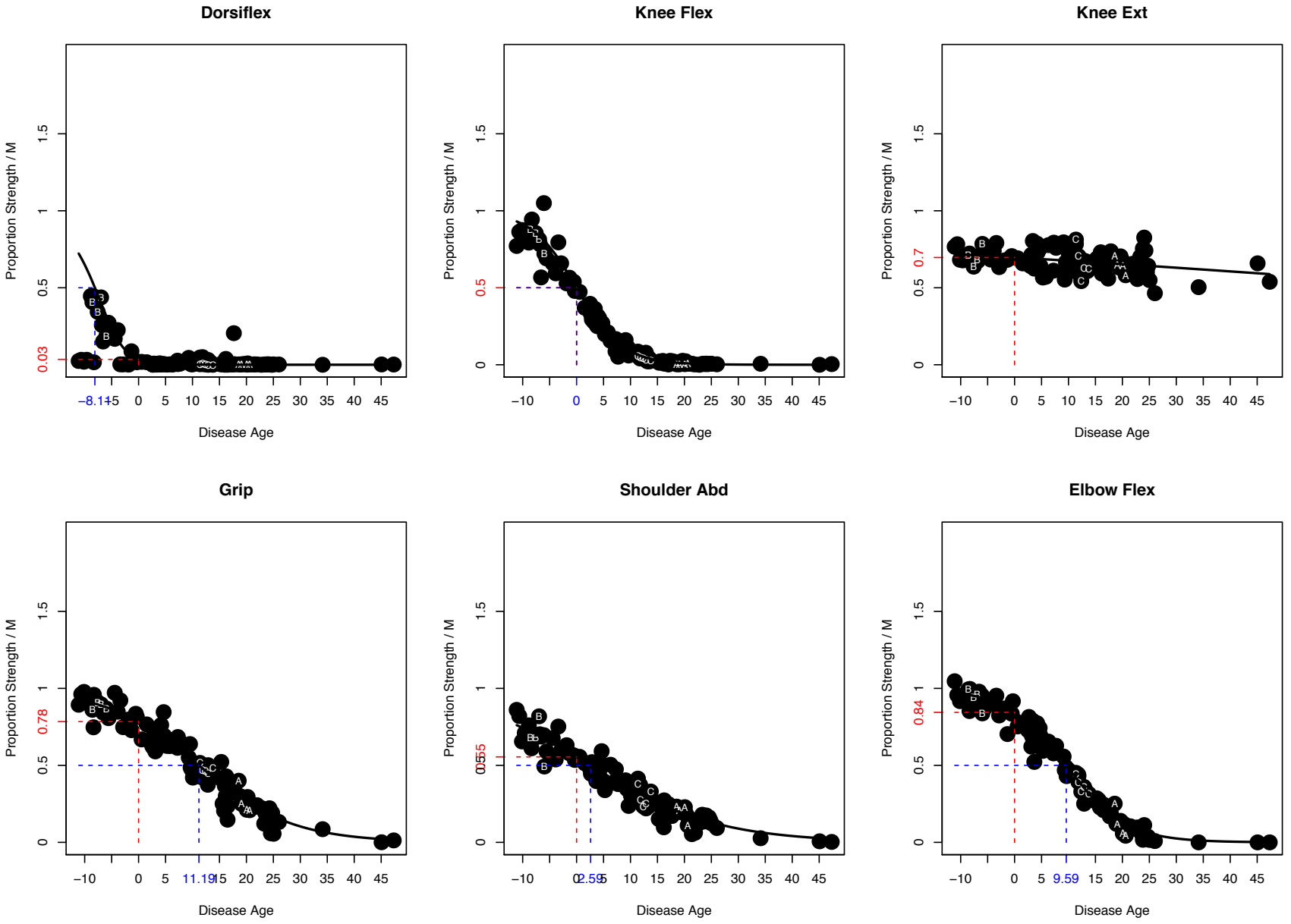

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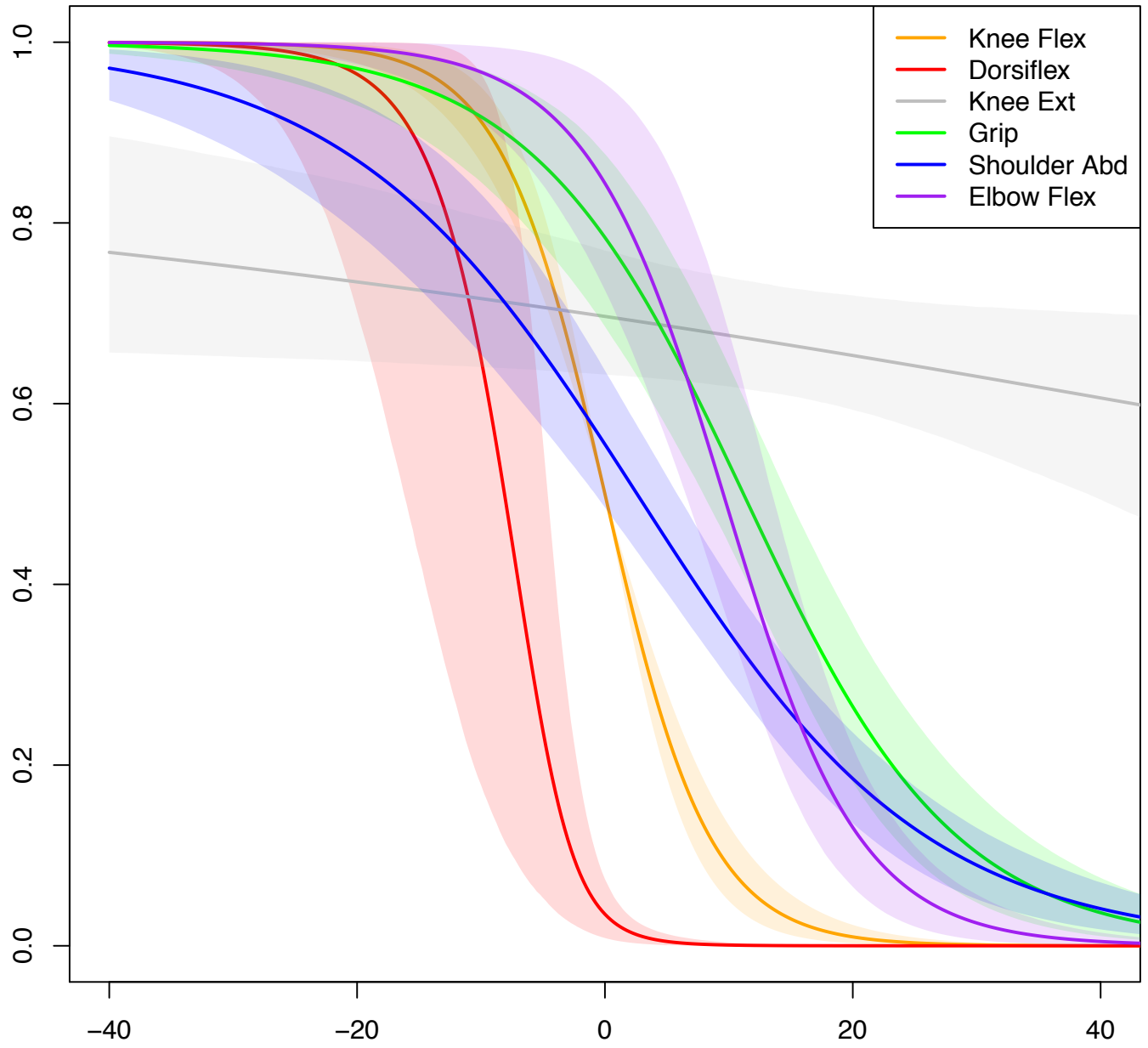

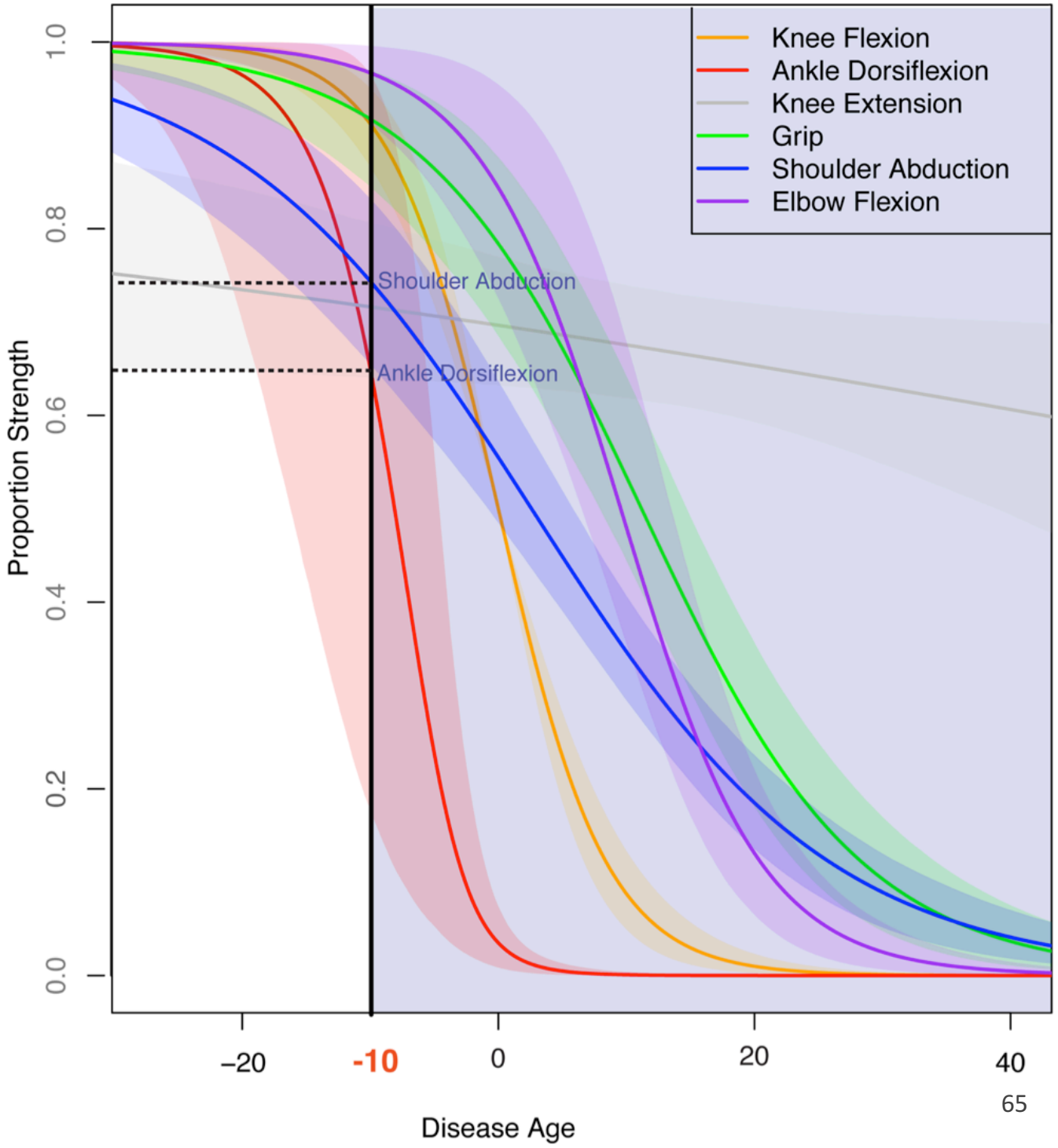
Knee Flexion
Ankle Dorsiflexion
Knee Extension
Grip
Shoulder Abduction
Elbow Flexion
Shoulder Abduction
Ankle Dorsiflexion
Proportion Strength
1.0
0.8
0.6
0.4
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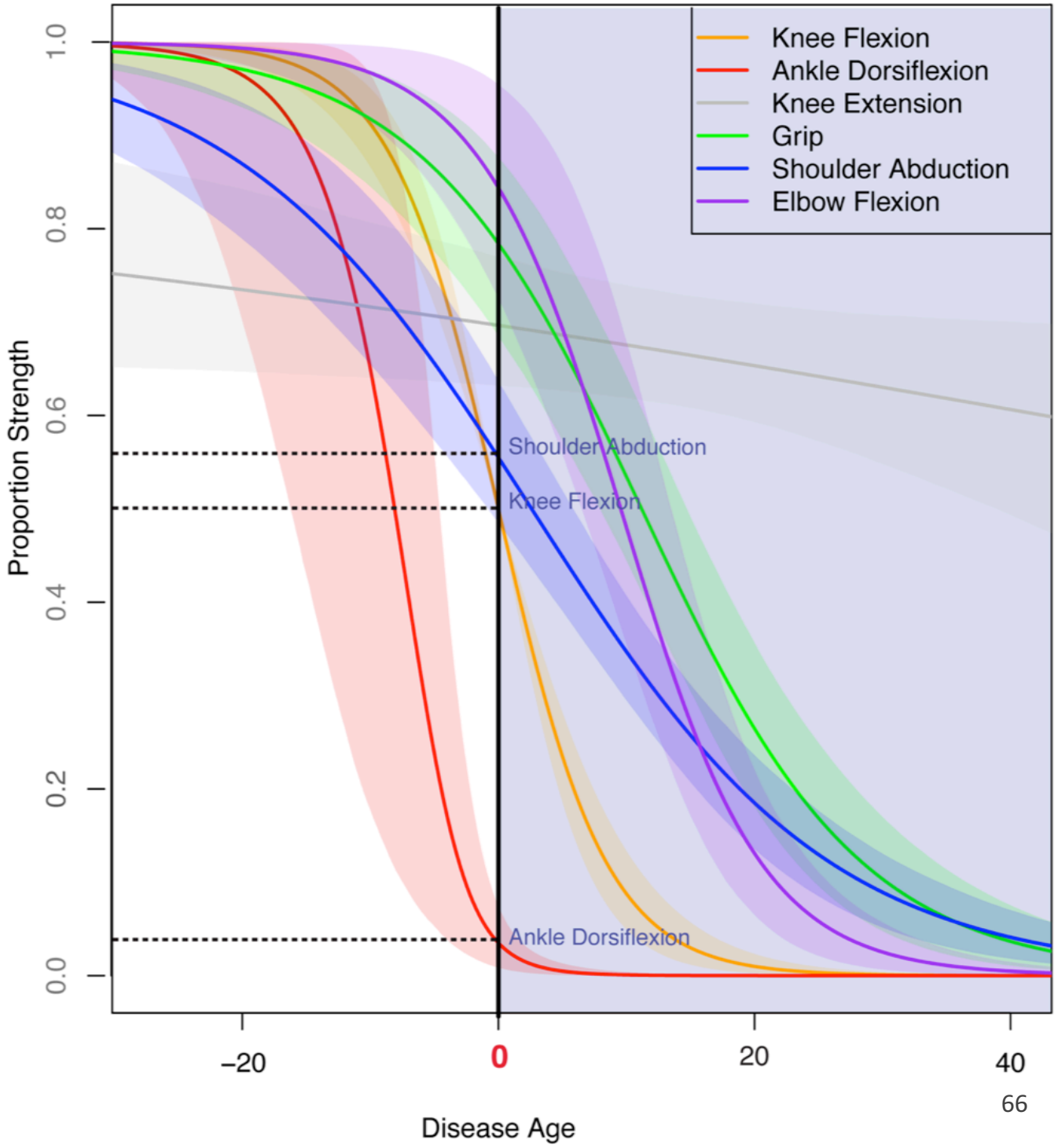
0.0
–20
-10
0
20
40
Disease Age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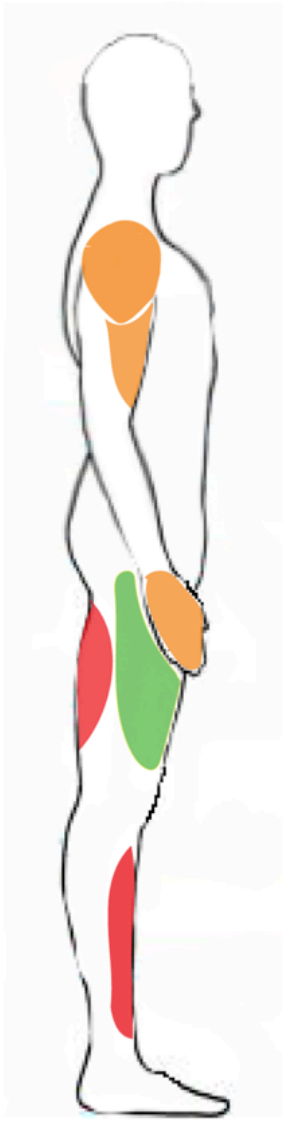

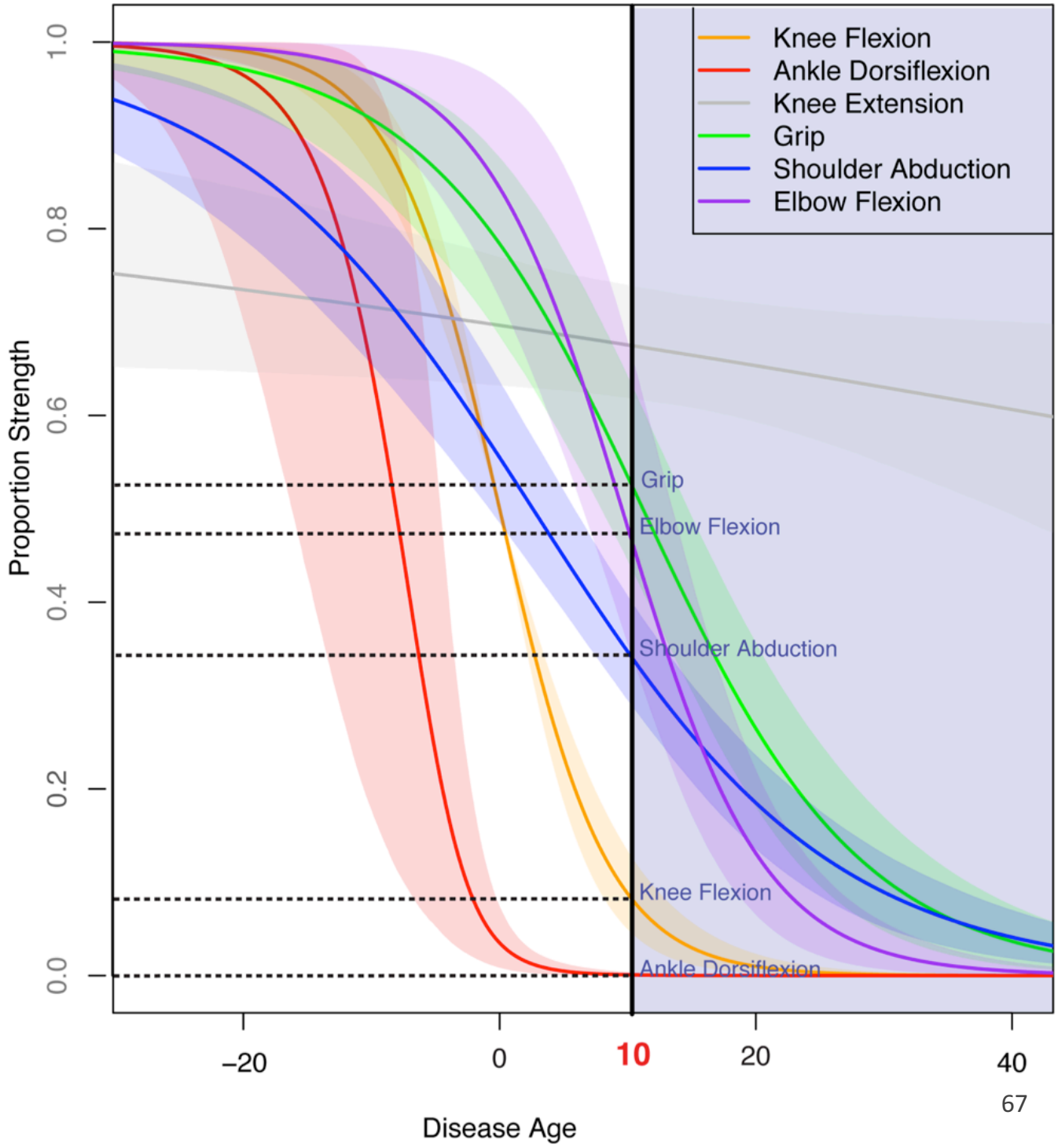
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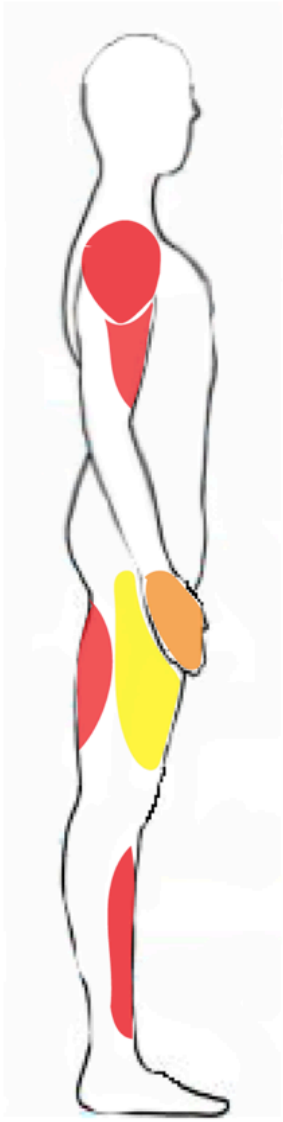

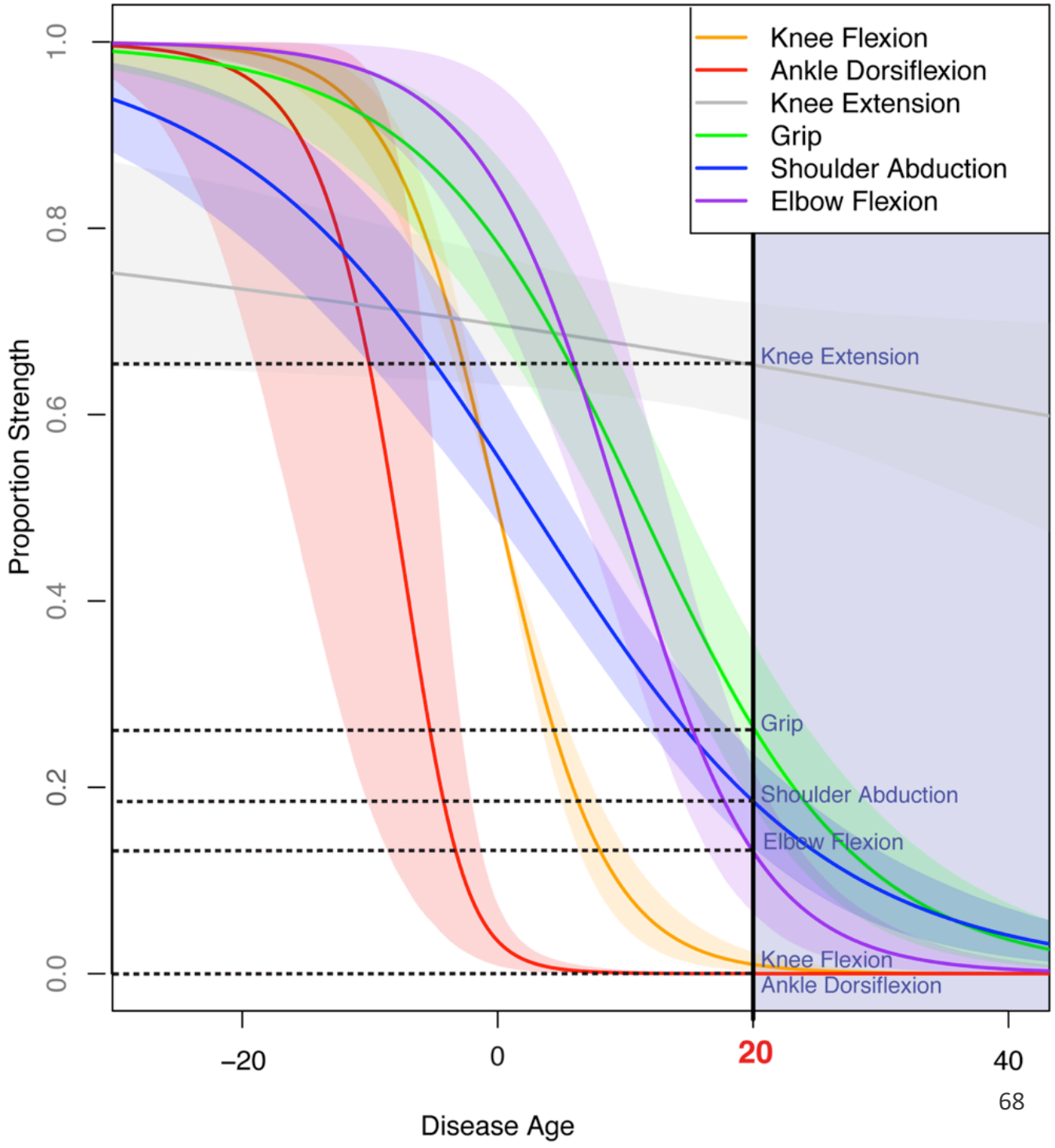
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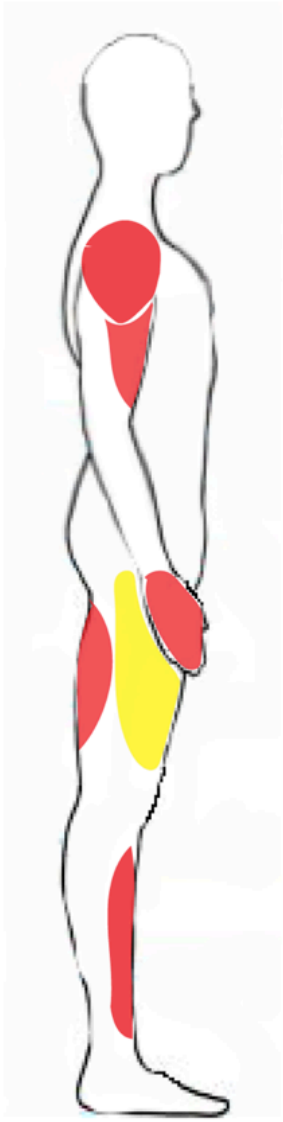

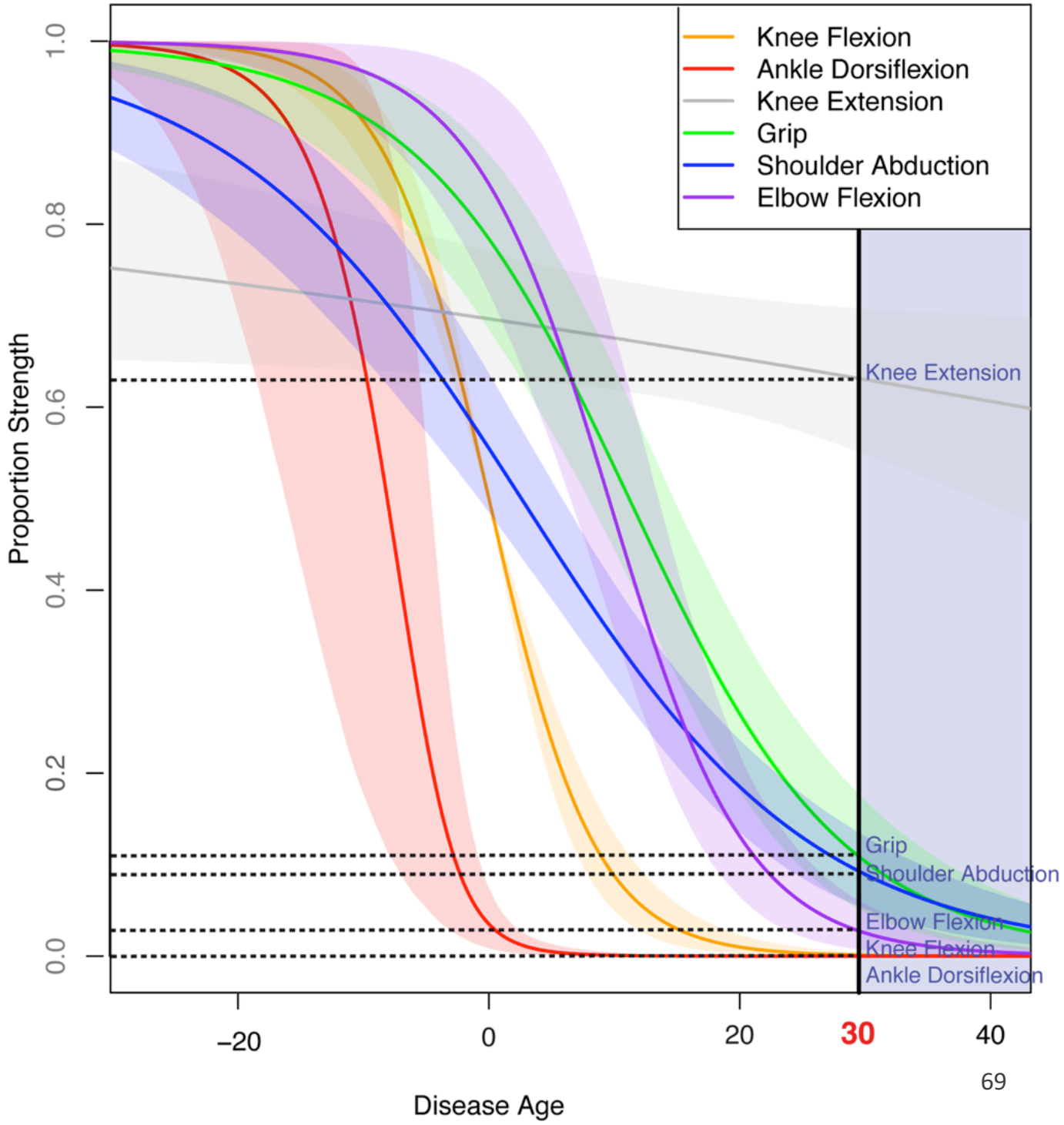
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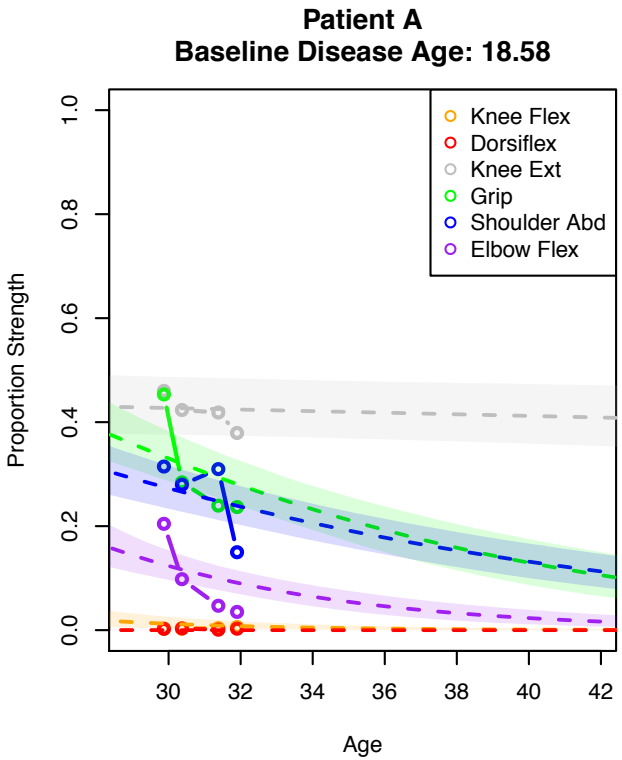
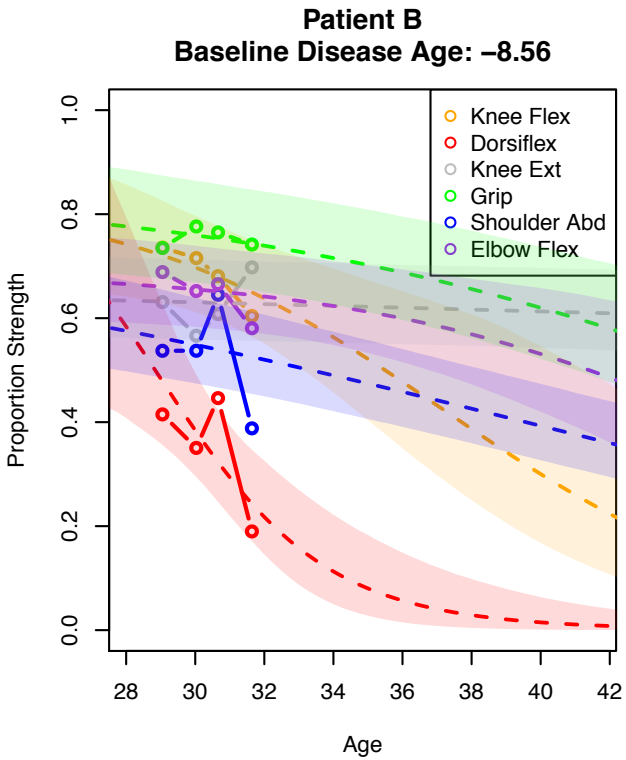
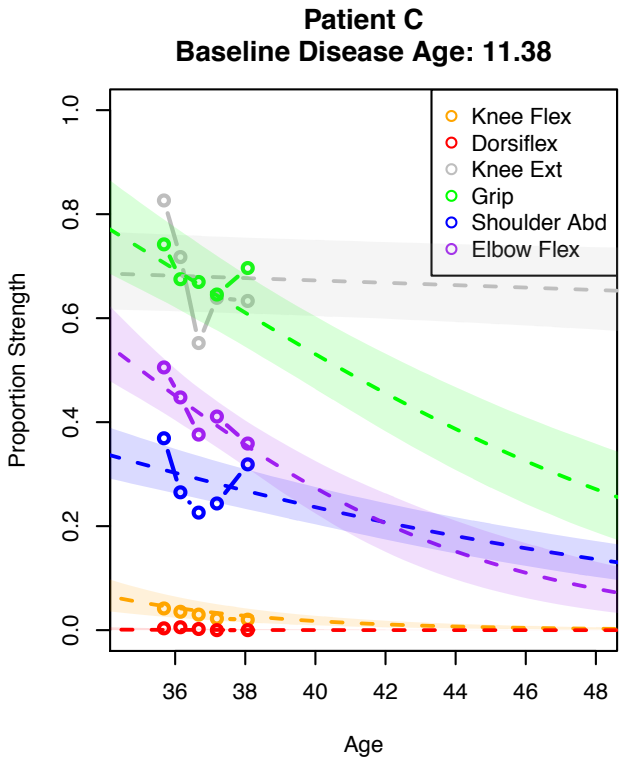
Disease Age

Patient-Specific Prediction



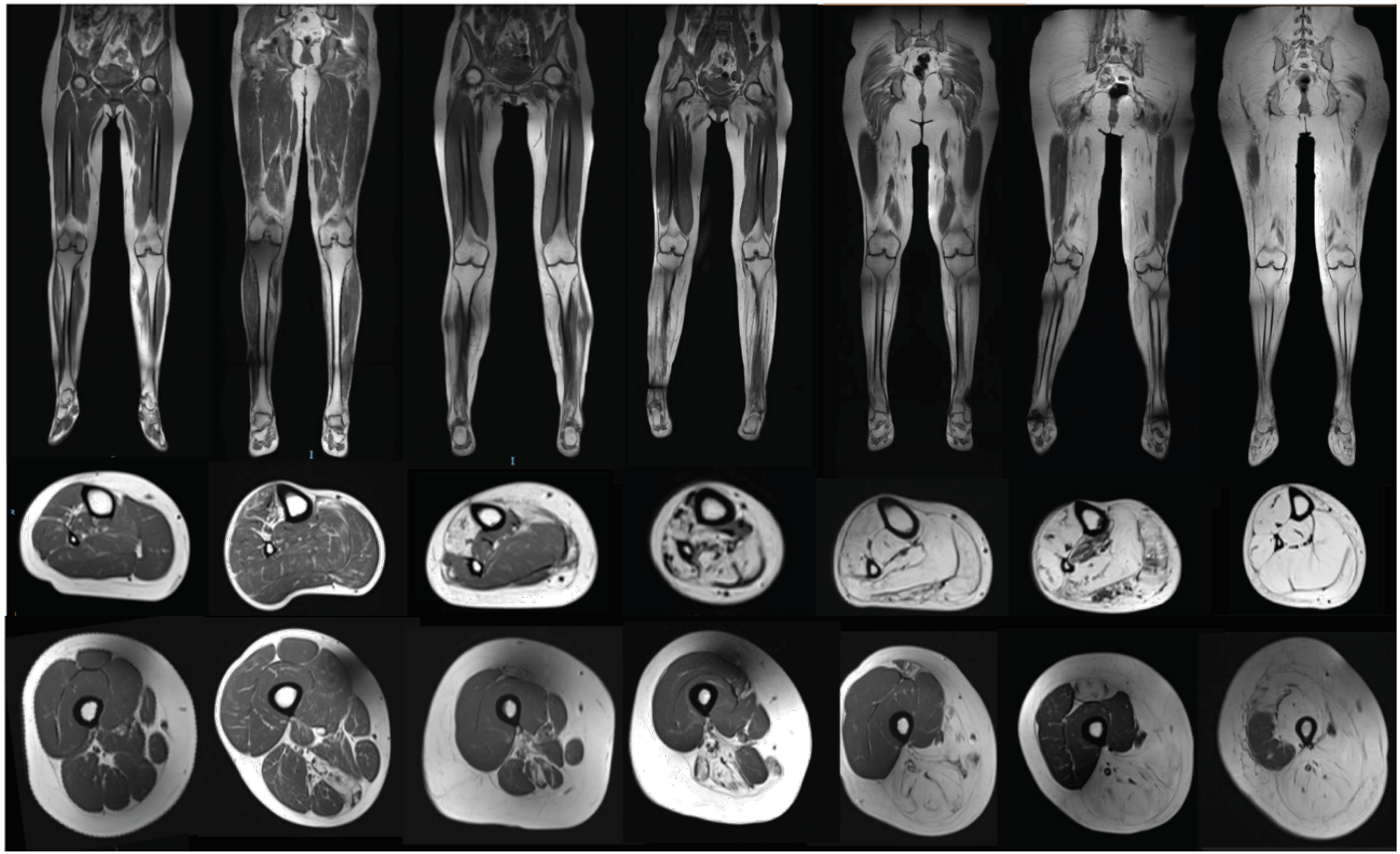




DISEASE PROGRESSION VS. CLINICAL MANIFESTATION

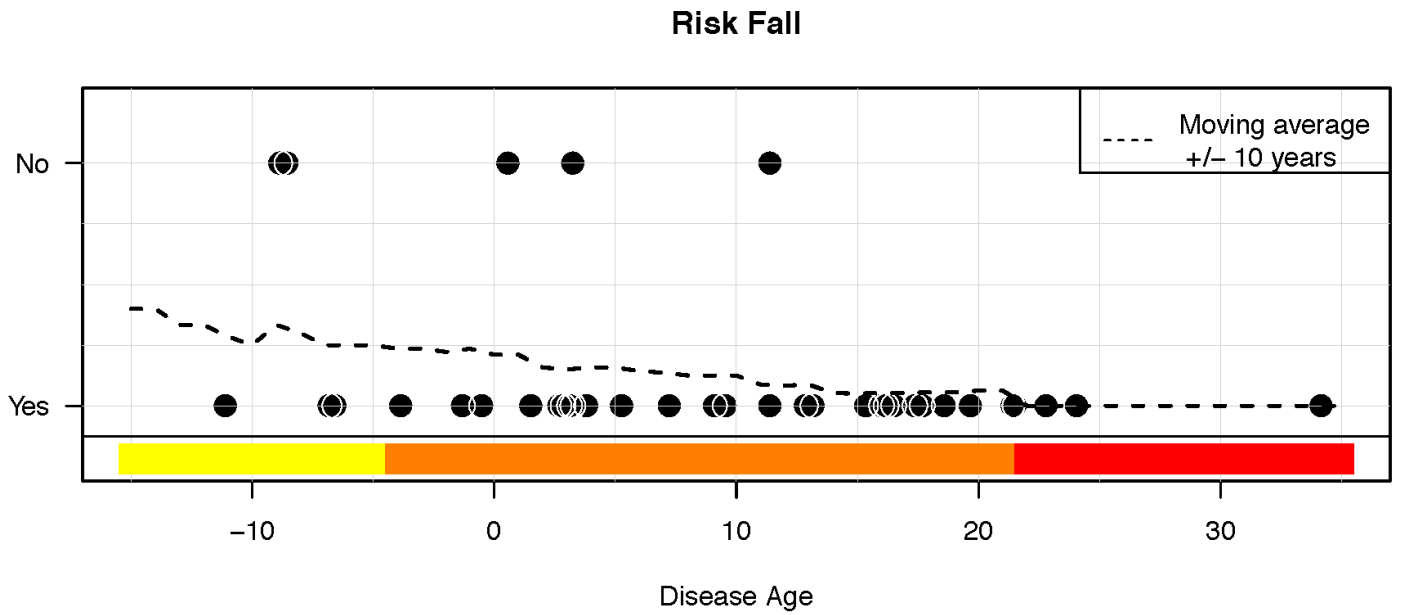
Disease Age vs. MRI

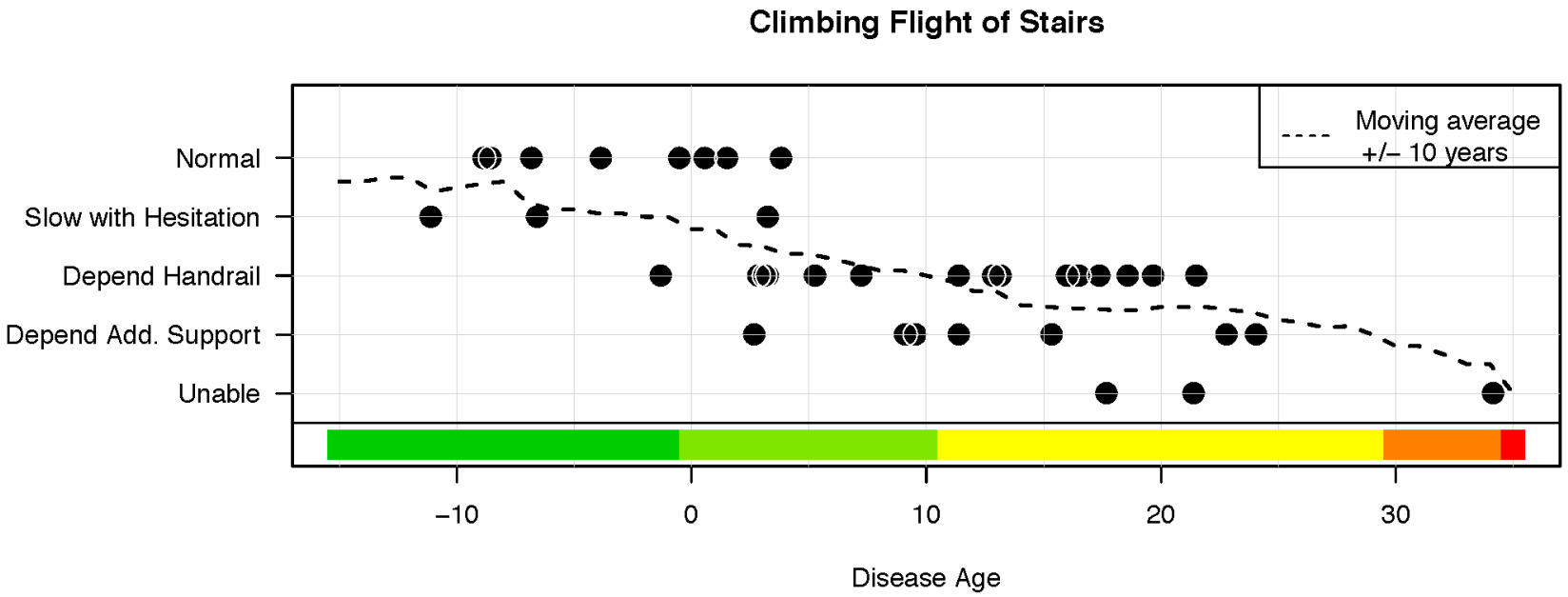
Est. Disease Age: **0** **1** **5** **10** **15** **17** **22**



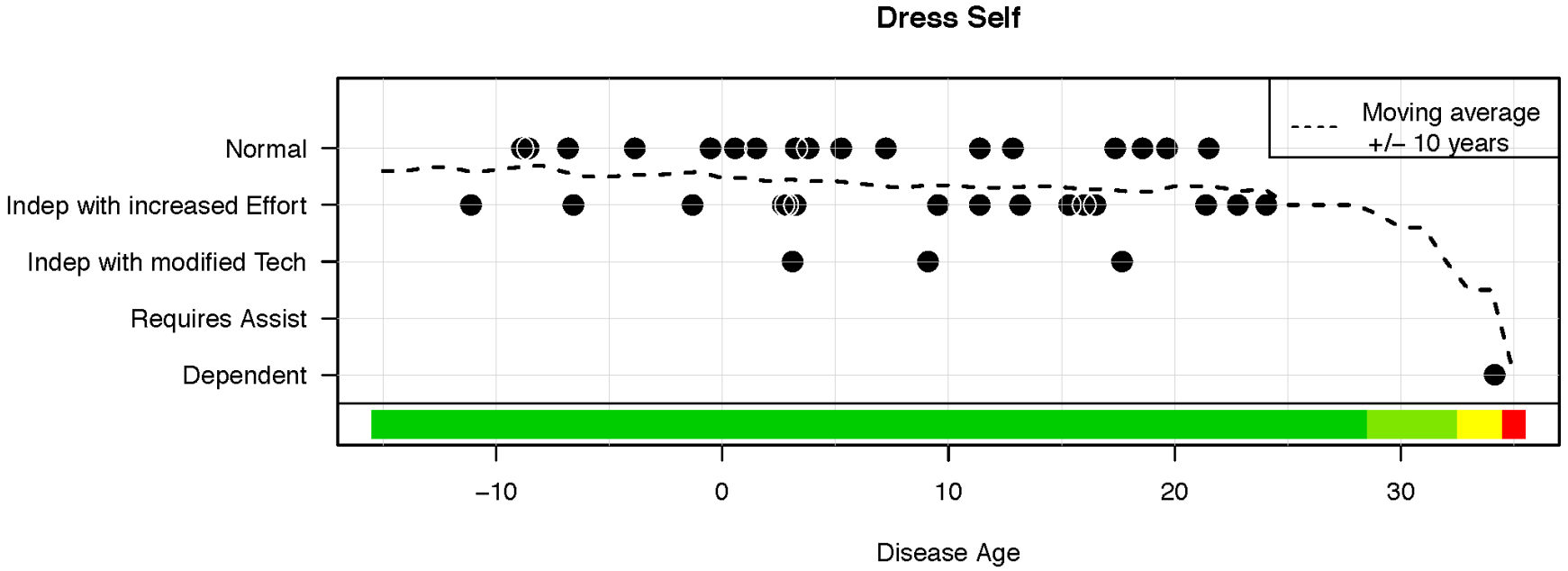
Courtesy of Carrillo-Carrasco

Disease Age vs. Clinical Manifestation

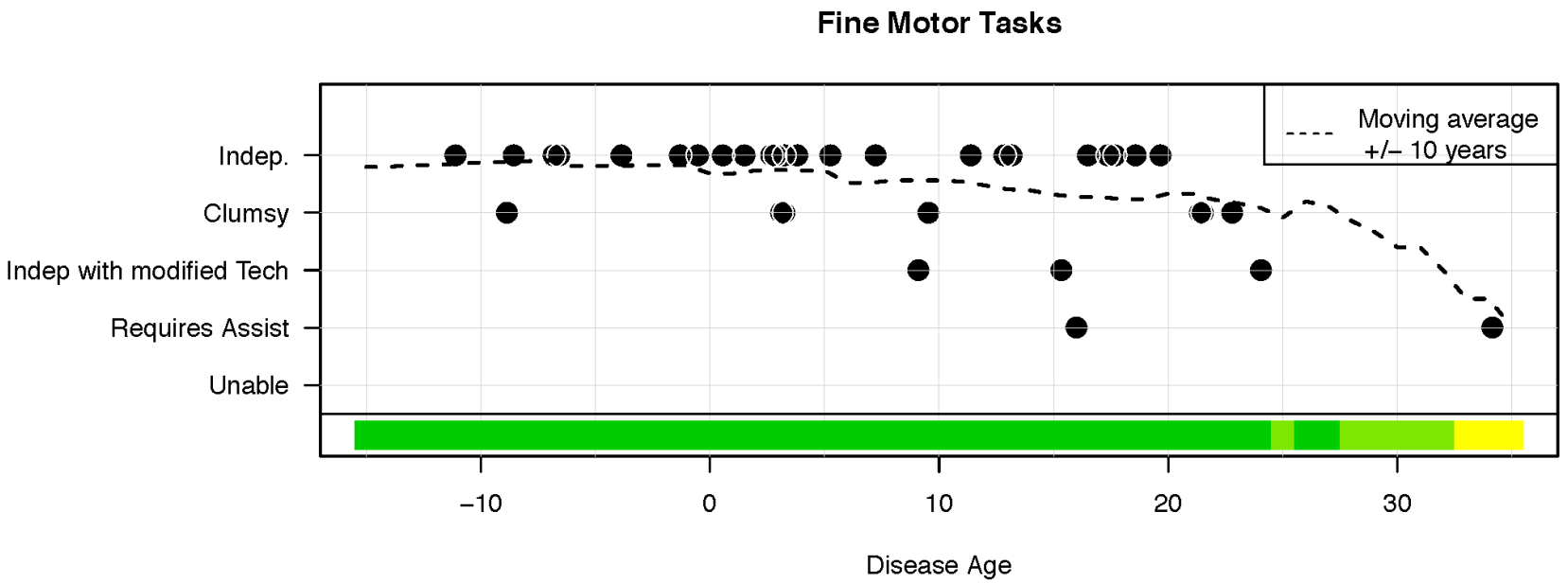


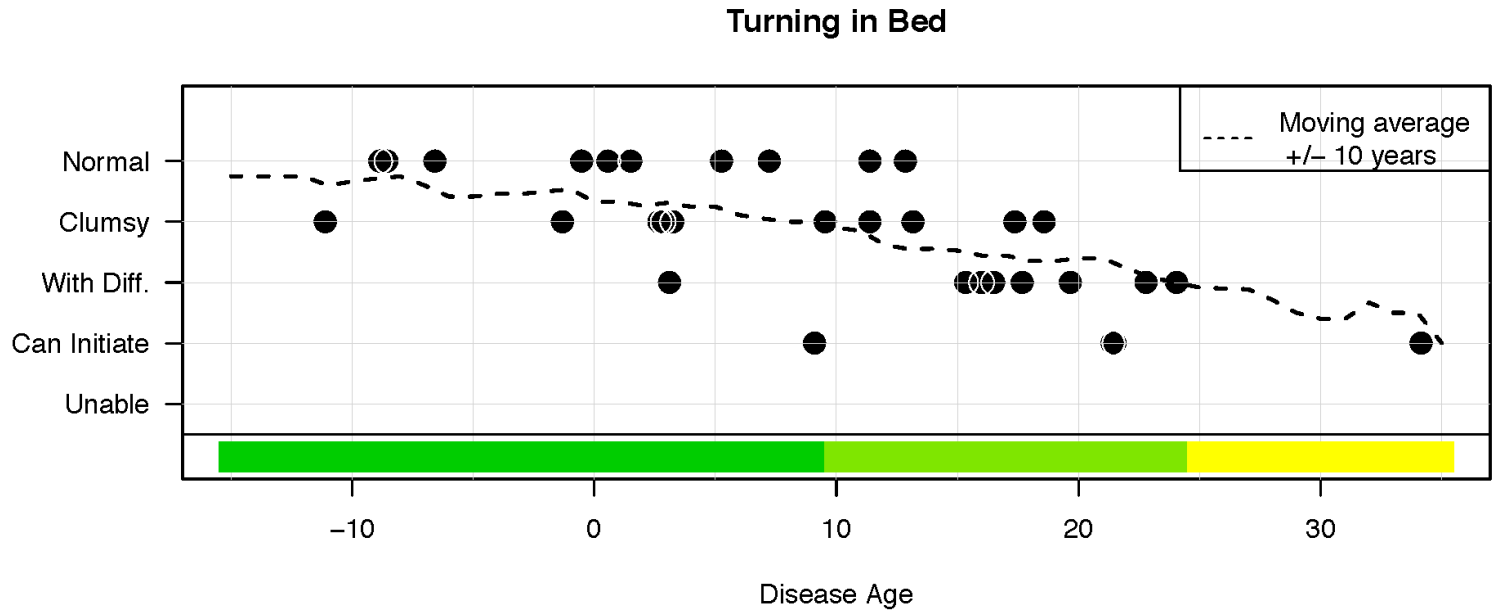


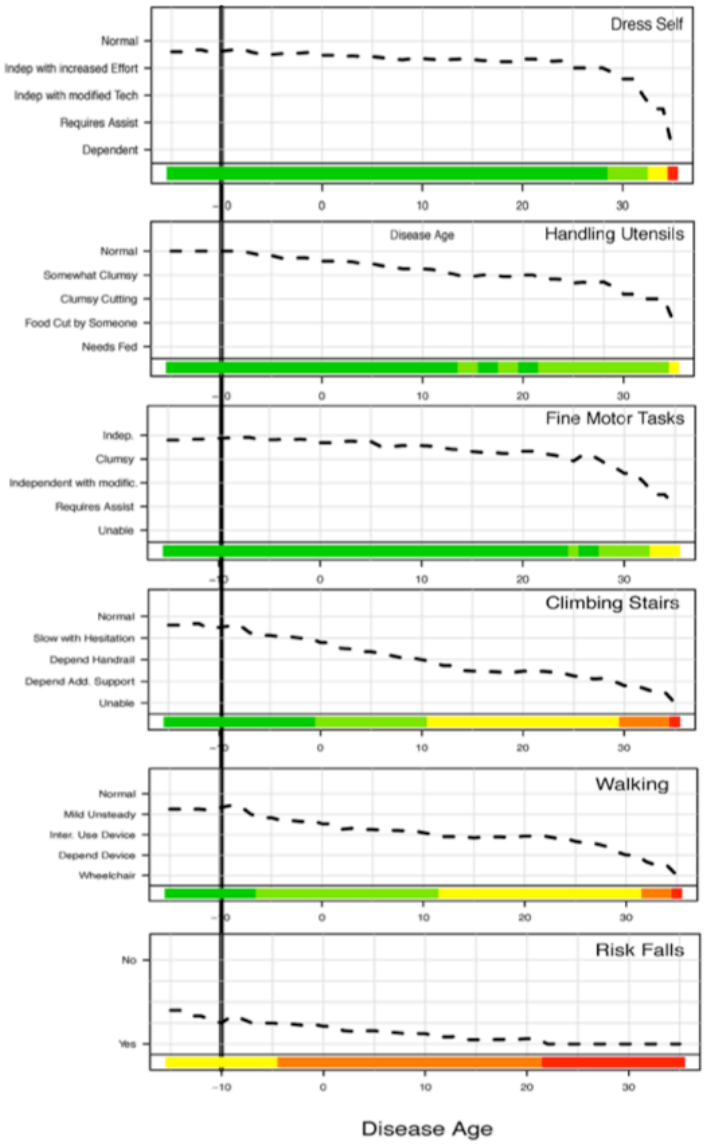
Disease Age vs. Clinical Manifestation

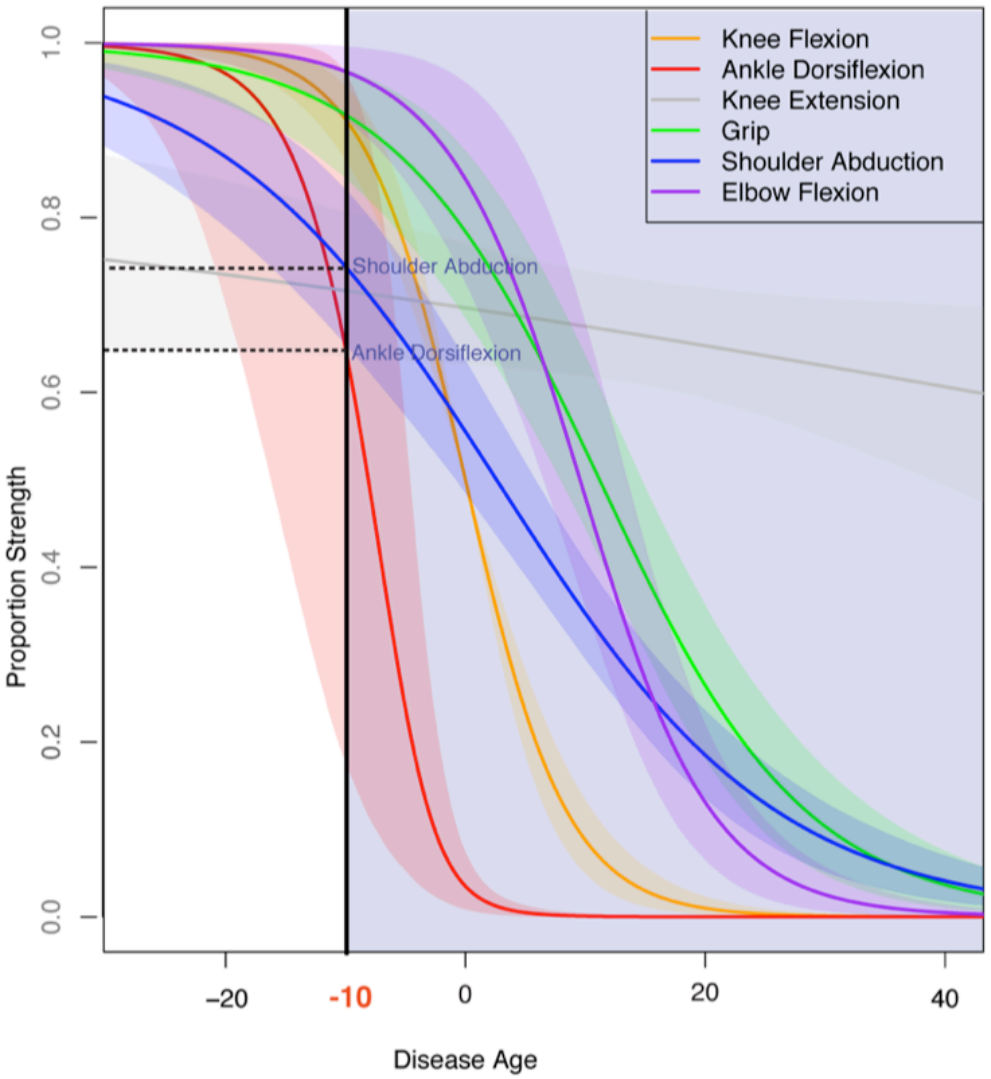


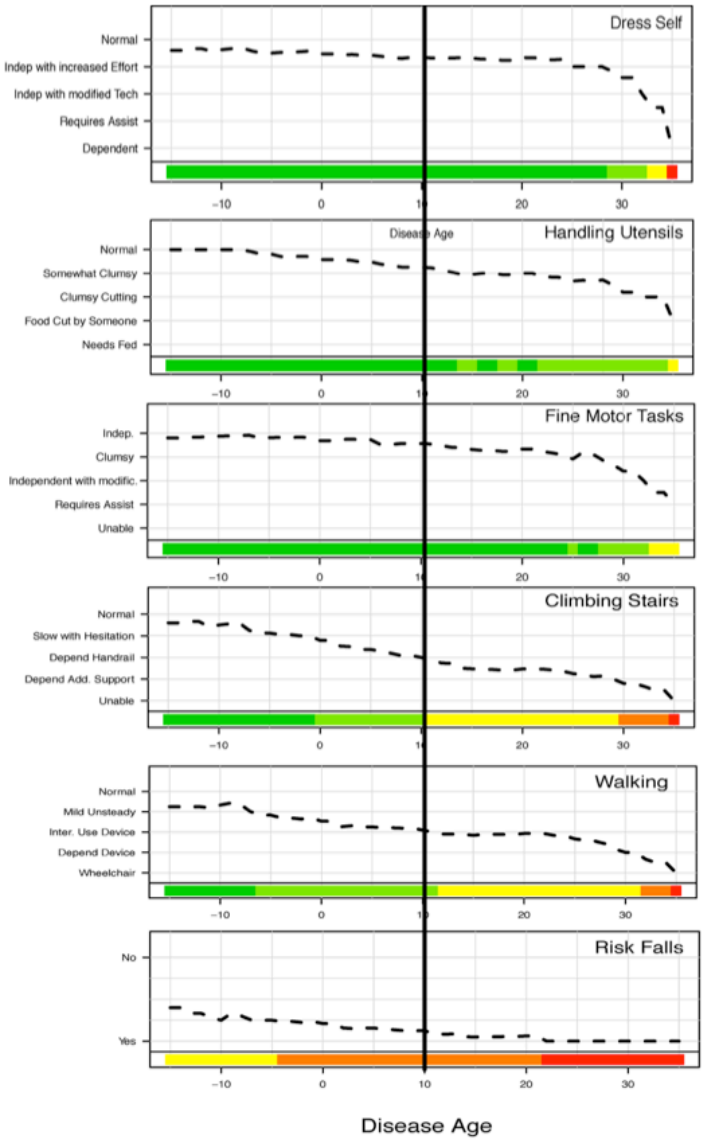
Disease Age vs. Clinical Manifestation






Dress Self
Normal
Indep with increased Effort
Indep with modified Tech
Requires Assist
Dependent
Handling Utensils
Disease Age
Normal
Somewhat Clumsy
Clumsy Cutting
Food Cut by Someone
Needs Fed
Fine Motor Tasks
Indep.
Clumsy
Independent with modific.
Requires Assist
Unable
Climbing Stairs
Normal
Slow with Hesitation
Depend Handrail
Depend Add. Support
Unable
Walking
Normal
Mild Unsteady
Inter. Use Device
Depend Device
Wheelchair
Risk Falls
No
Yes
−10
0
10
20
30
Disease Age


Knee Flexion
Ankle Dorsiflexion
Knee Extension
Grip
Shoulder Abduction
Elbow Flexion
Shoulder Abduction
Ankle Dorsiflexion
Proportion Strength
0.0
0.2
0.4
0.6
0.8
1.0
−20
-10
0
20
40
Disease Age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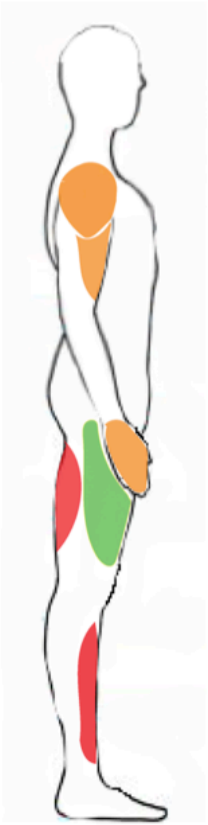

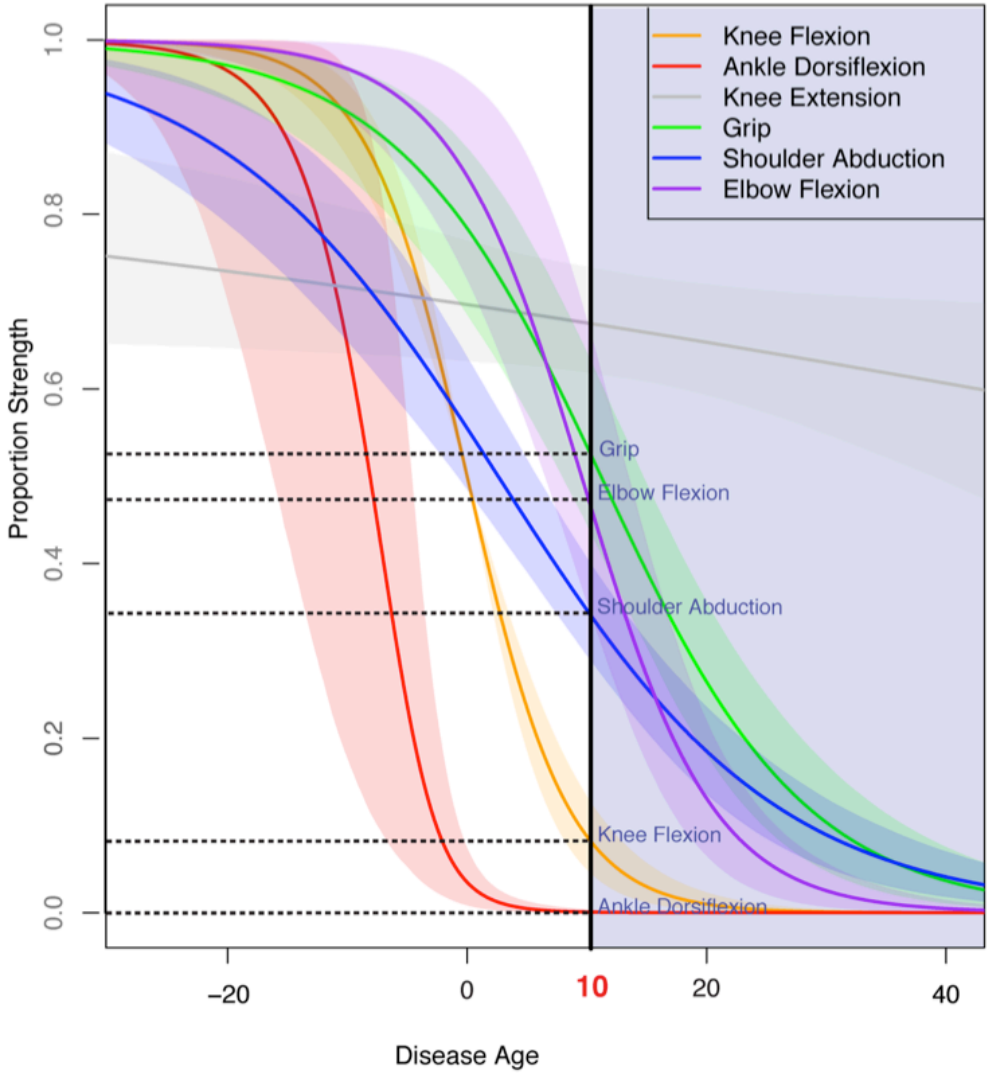
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Disease Age

DETERMINE EFFECT OF NOVEL THERAPIES

Incorporation of Treatment Effect

$$Y_{i,j,k} \sim N(\mu_{i,j,k}, (\sigma_k \mu_{i,j,k})^2 + \delta)$$

$$\mu_{i,j,k} = \begin{cases} \text{logit}^{(-1)}[\theta_k + \beta_k (t_{i,j} - \alpha_i)] * M_{i,k} & \text{pre-treatment} \\ \text{logit}^{(-1)}[\theta_k + \beta_k \gamma (t_{i,j} - T_i)] * M_{i,k} & \text{post-treatment} \end{cases}$$

Time of treatment subject i

Treatment effect: Constant % slowing in the rate of decline across all muscles under treatment compared to the rate of decline in the placebos

- Alt. interpretation: Slowing in number of years it will take to reach milestones
  - Ex: 50% slowing in rate of decline = will take subject 2x's as many years to reach milestone under treatment

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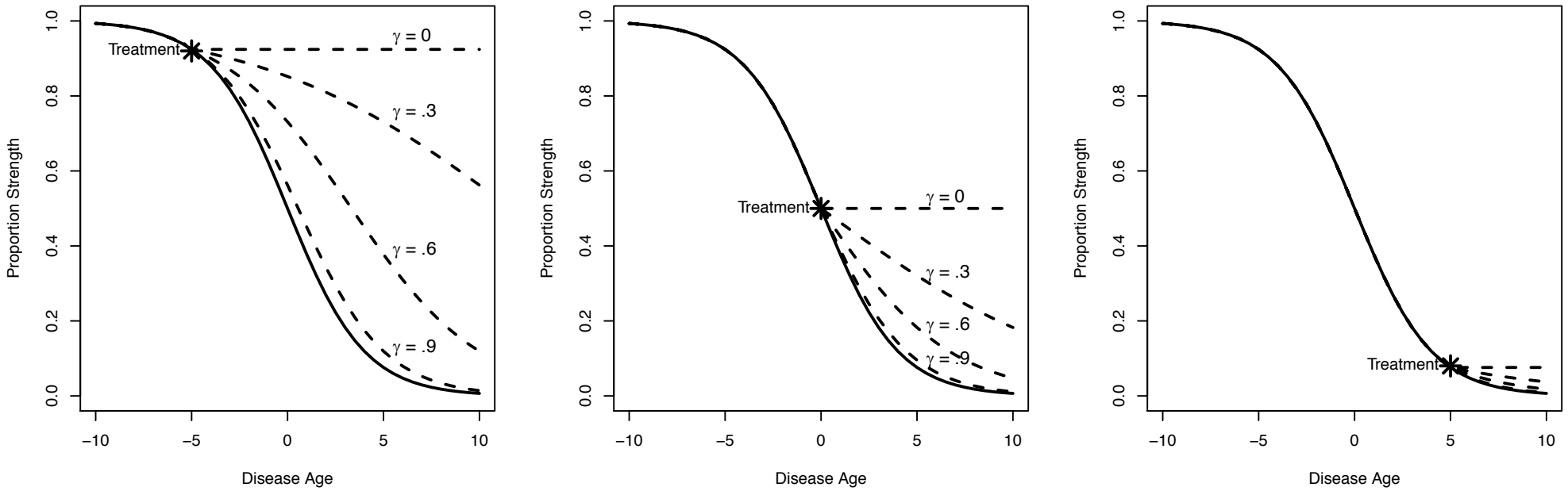
Incorporation of Treatment Effect



- Ability to detect treatment effect depends are where the patient is on the decline
- Muscle where we can best detect treatment effect is subject-specific
  - Given the patients disease age, which muscle is actively decaying
- Incorporate all muscles in the estimation of treatment effect

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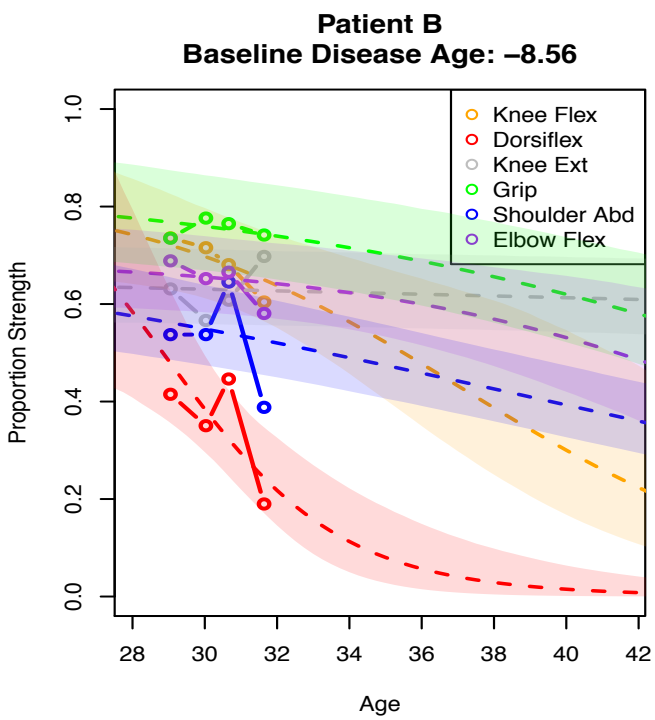
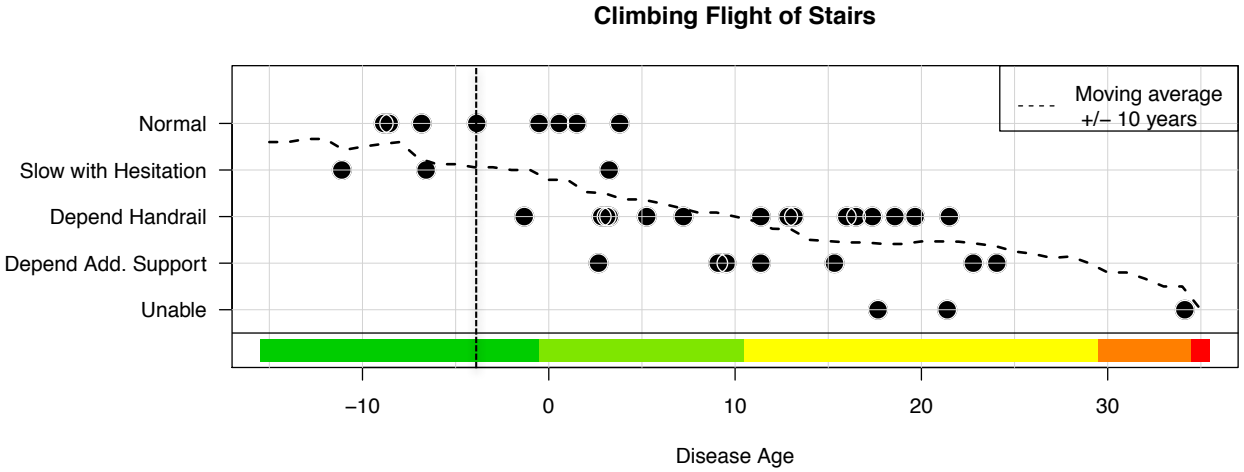
50% Reduction in Decline





	Natural Progression	Treatment*
Proportion of knee flexion strength (0.60->0.20)	42 years old	52 years old
Ability to climb stairs: Dependent on a handrail	47 years old	62 years old
Ability to walk: Intermittent use of an ambulatory device	47 years old	62 years old

**Slow Decline by 50% with γ= 0.5*

CLINICAL TRIAL SIMULATIONS

Clinical Trial Design + Simulation

- **Primary Endpoint:** Disease Progression Model
- **Incorporate natural history data**
- **Key Design Questions:**
  - How many new patients should we enroll?
  - Should we enroll additional controls:
    - Compare power under 1:1, 3:1 and single arm trial
  - How long of follow-up do we need on each patient?
  - How often should we plan visits?

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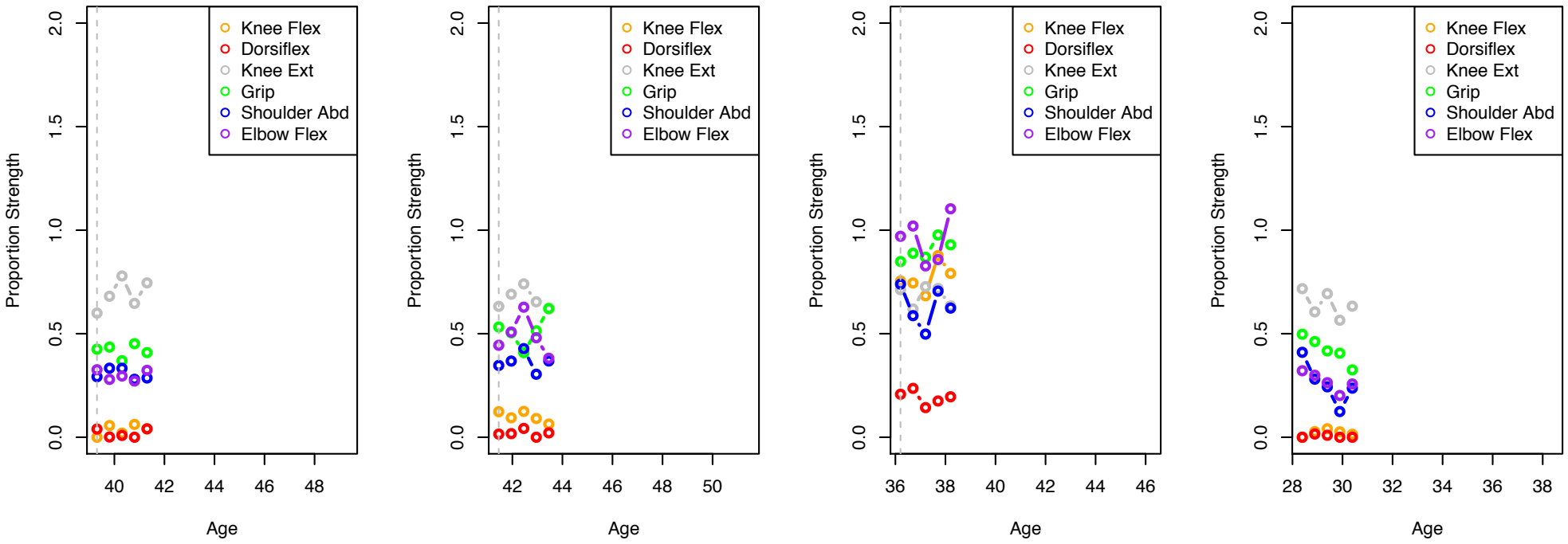
Clinical Trial Design: Clinical Trial Simulations

- **Design trial and answer key questions by simulation**
- **Use disease progression model as virtual patient simulator**
- **Simulation Assumptions:**
  - Sample Size: 50 Patients
  - Distribution of Disease age & Muscle Decay Parameters: Same as in natural history patients
  - Visits: Every 6 months
  - Randomization: 1:1, 3:1 or All:None
  - Post-treatment follow-up: 1, 1.5, or 2 years of follow-up
  - Possible treatment effects:
    - γ=0: treatment completely stops decline
    - γ=.25: treatment reduces rate of decline by 75%
    - γ=.5: treatment reduces rate of decline by half
    - γ=1: treatment does not reduce rate of decline

Clinical Trial Design: Clinical Trial Simulations



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Clinical Trial Design: Clinical Trial Simulations

		Power		
		1:1	**3:1**	**All : None**
1 year post	γ=0	0.65	0.79	0.90
	γ=.25	0.38	0.56	0.74
	γ=.5	0.36	0.36	0.49
	γ=1	0.07	0.07	0.03
1.5 years post	γ=0	0.97	1.00	1.00
	γ=.25	0.92	0.90	0.98
	γ=.5	0.47	0.68	0.75
	γ=1	0.03	0.04	0.03
2 years post	γ=0	1.00	1.00	1.00
	γ=.25	0.98	1.00	1.00
	γ=.5	0.81	0.90	0.93
	γ=1	0.04	0.06	0.06

Summary

- **Disease Progression Modeling + Clinical Trial Simulation = More informed decision making**
- **Disease progression primary analysis models**
  - Capture multiple aspects and varying stages of the disease… not just one
  - Adjust for expected natural rate of decline vs. enriching to include only those likely to decline
  - Especially important in rare disease
    - Limited patient resources… we should not limit this more
- **Word of caution: Work closely with clinicians**
  - Statisticians have no problem developing extremely complex models
  - Model inputs and outputs need to be clinically meaningful

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