National Institute on Aging
Intramural Research Program

Toward identification of optimal outcomes:
Characterizing long-term biomarker and cognitive trajectories

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ISCTM

Prevention Trials of Alzheimer's Disease – Ongoing Optimization and the Roles of Biomarkers and Cognitive, Performance, and Functional Assessments

Working Group Dinner

Alzheimer's Disease begins years before diagnosis

- Over 5 million in the U.S. with Alzheimer's
- Currently no cure or preventive intervention

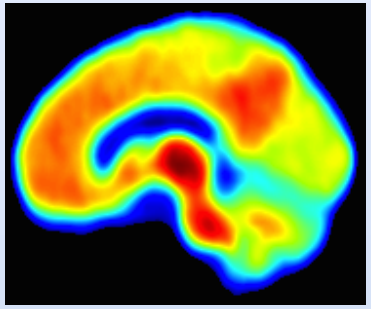
> 10 years, estimated

Window for therapeutic intervention to prevent / delay disease

Preclinical stage 1

Neuropathology

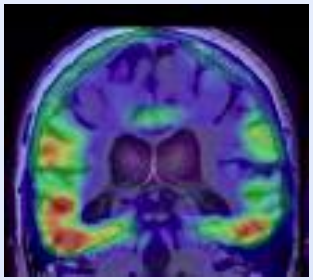
Amyloid beta plaques

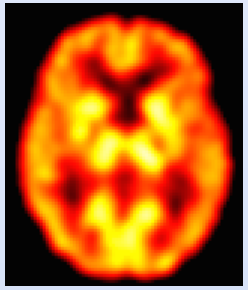


Preclinical stage 2

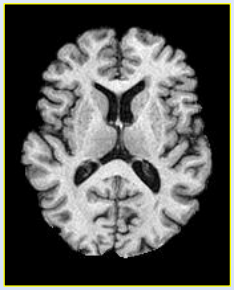
Neurodegeneration

Tau tangles





Alterations in brain function

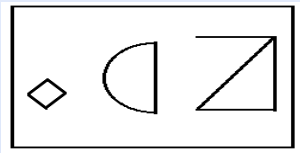


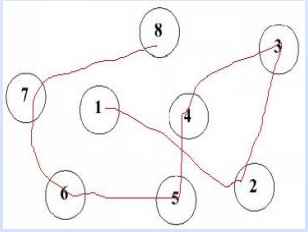
Structural brain changes

Preclinical stage 3

Subtle cognitive decline

Declines on neuropsychological testing





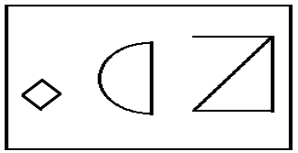
Mild cognitive impairment

Dementia due to Alzheimer's

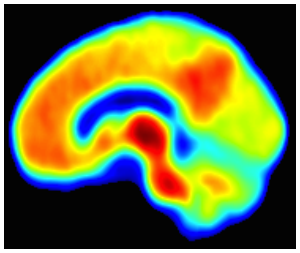
Progression Score Model

Long-term trajectories from shorter-term observations

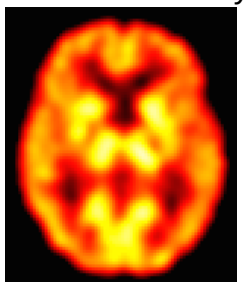
Cognitive scores



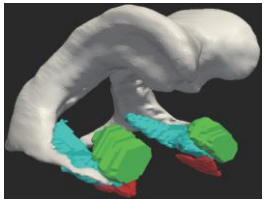
Amyloid

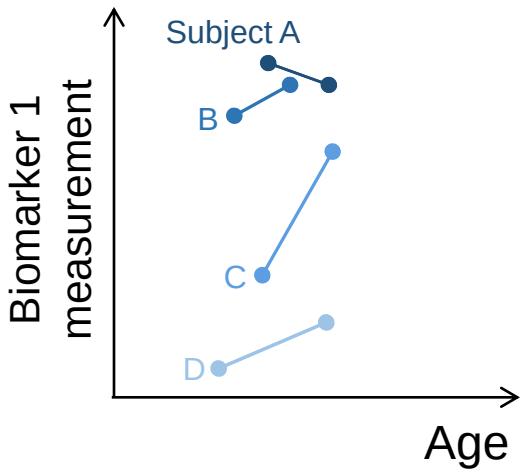


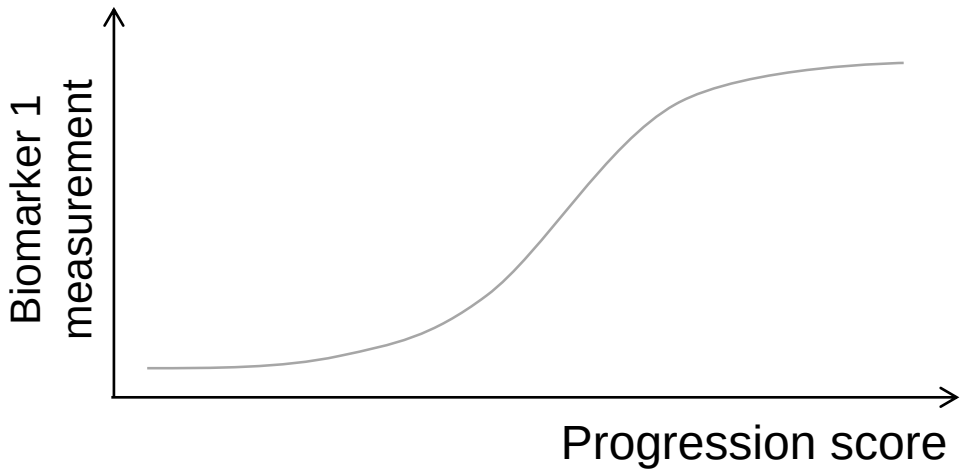
Functional activity

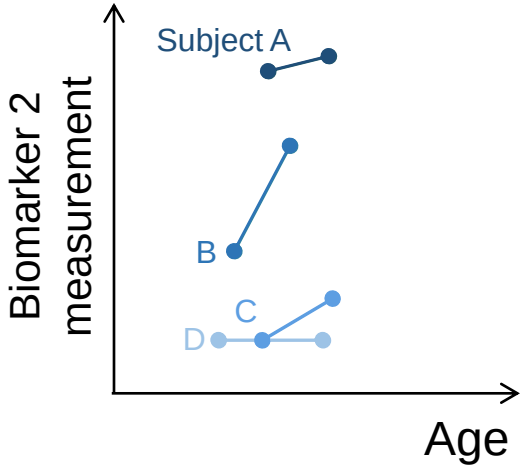


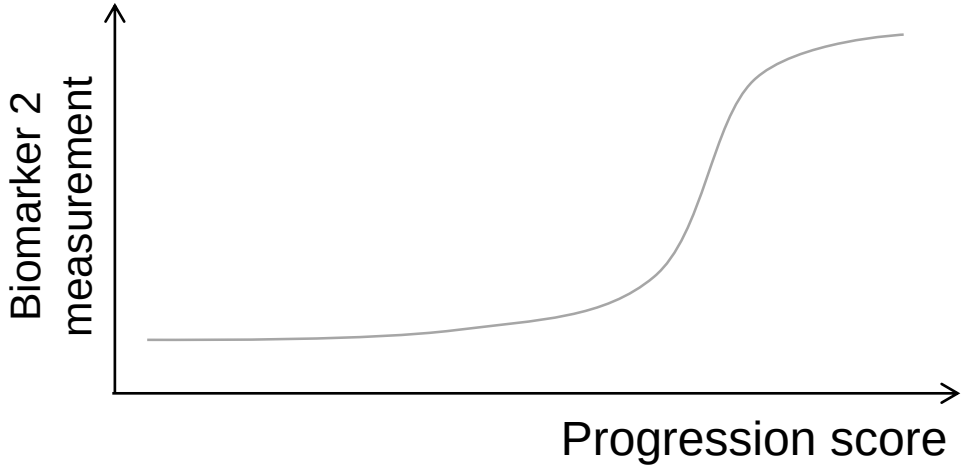
Volumetrics





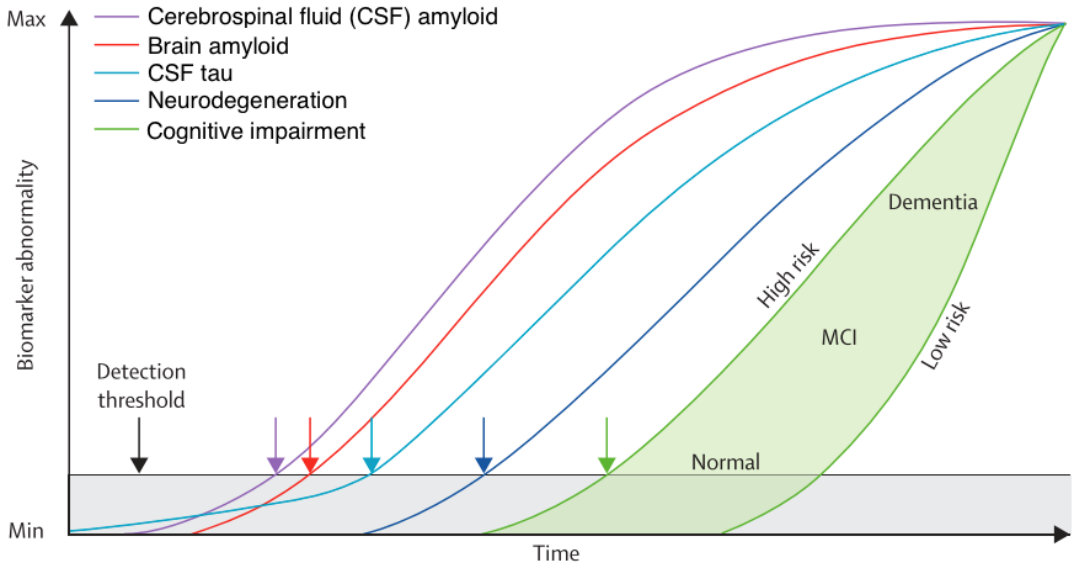




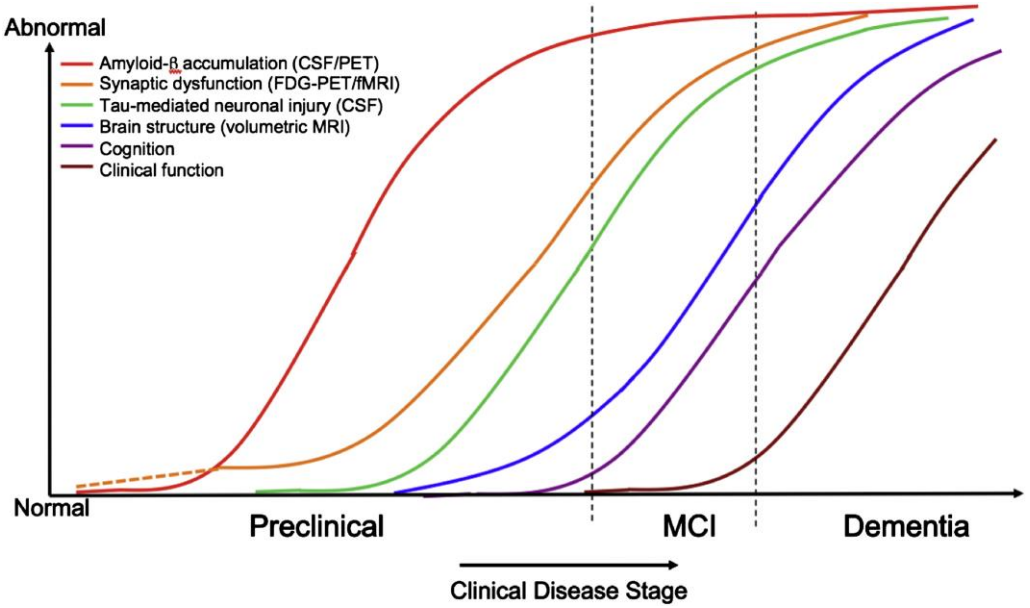


Bilgel et al., A multivariate nonlinear mixed effects model for longitudinal image analysis: Application to amyloid imaging, NeuroImage 2016.

Hypothetical models of AD progression



Jack et al., "Tracking pathophysiological processes in Alzheimer's disease," Lancet Neurology 12 (2), 2013.



Sperling et al., "Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease," Alzheimer's & Dementia 7(3), 2011.

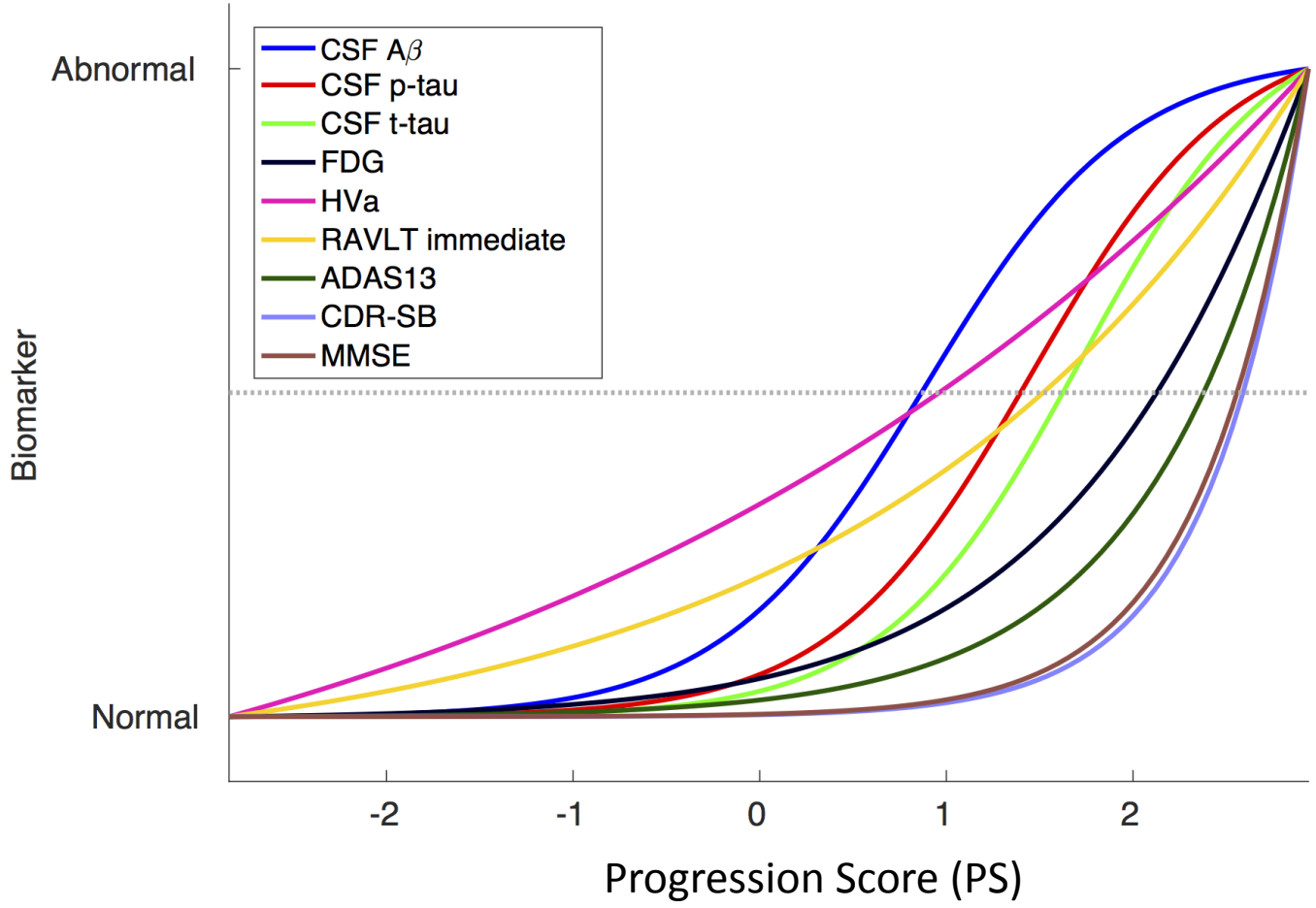
Participants

	NL n = 477	MCI n = 625	Dementia n = 603
Age at last visit, mean (SD), y **Range**	76.4 (6.6) 58.2 – 95.6	75.7 (7.9) 54.4 – 93.4	76.6 (7.6) 55.1 – 92.2
Female, no. (%)	246 (51.6%)	261 (41.8%)	251 (41.6%)
Education, mean (SD), y **Range**	16.5 (2.7) 6 – 20	15.9 (2.9) 4 – 20	15.5 (2.9) 4 – 20
Number of visits, mean (SD) **Range**	4.0 (2.1) 1 – 11	4.0 (1.9) 1 – 11	3.9 (2.0) 1 – 11
Follow-up duration, mean (SD), y **Range**	2.8 (2.1) 0 – 10.0	2.5 (1.8) 0 – 9.1	2.1 (1.8) 0 – 9.1

Biomarkers and cognitive measures analyzed:

- CSF Aβ, p-tau, t-tau
- FDG-PET
- Hippocampal volume (ICV adjusted)
- RAVLT immediate recall
- ADAS13, CDR-SB, MMSE

Temporal quantitative template



How can the Progression Score Model be useful for clinical trials?

1. Selection of optimal outcome measures
2. Recruitment of homogeneous samples
3. Individualized baselines against which to evaluate interventions

1. Selection of optimal outcome measures

Objective: Find the *optimal* set of *N* measures among a collection of biomarkers and cognitive measures.

- Define *optimal*:

a) Yields maximum separation between diagnostic groups

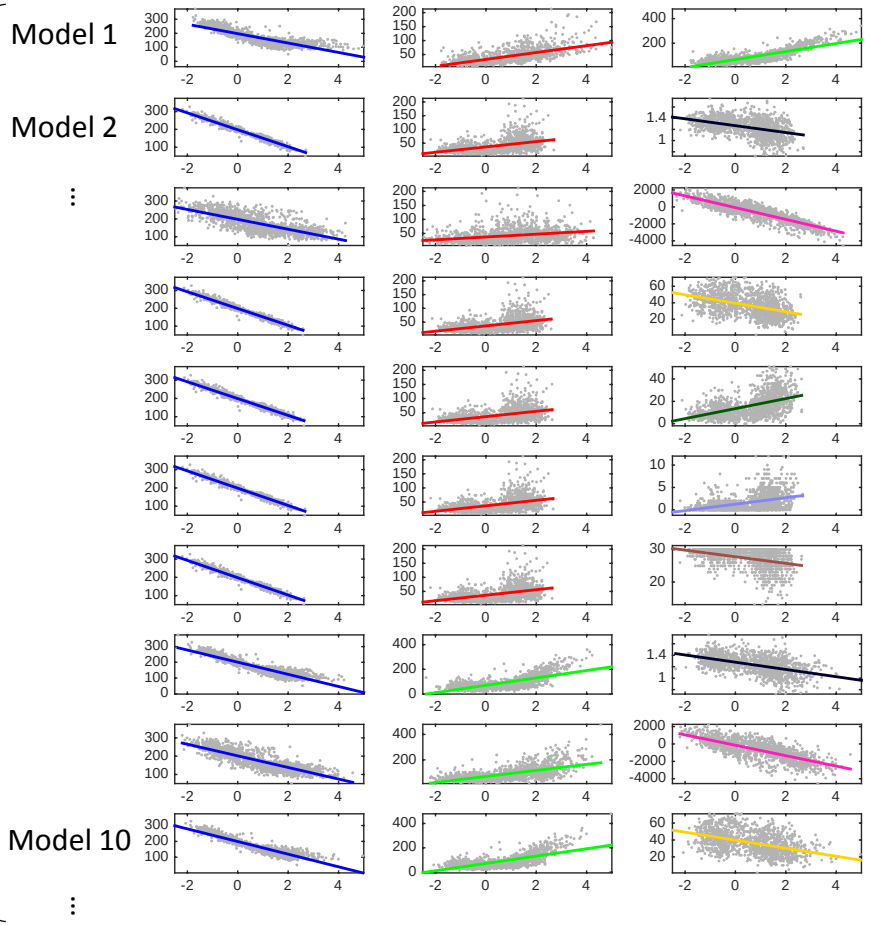
b) Maximizes confidence in the progression score estimated for each individual

c) Requires smallest sample size for detecting longitudinal effect

d) etc.

1. Selection of optimal outcome measures

Fit model for each possible combination of *N*=3 measures among 9



a) Maximize separation between diagnostic groups

- Compute effect size (Cohen's *d*) to assess difference in progression score at last visit between groups
- Top four models for each pairwise comparison:

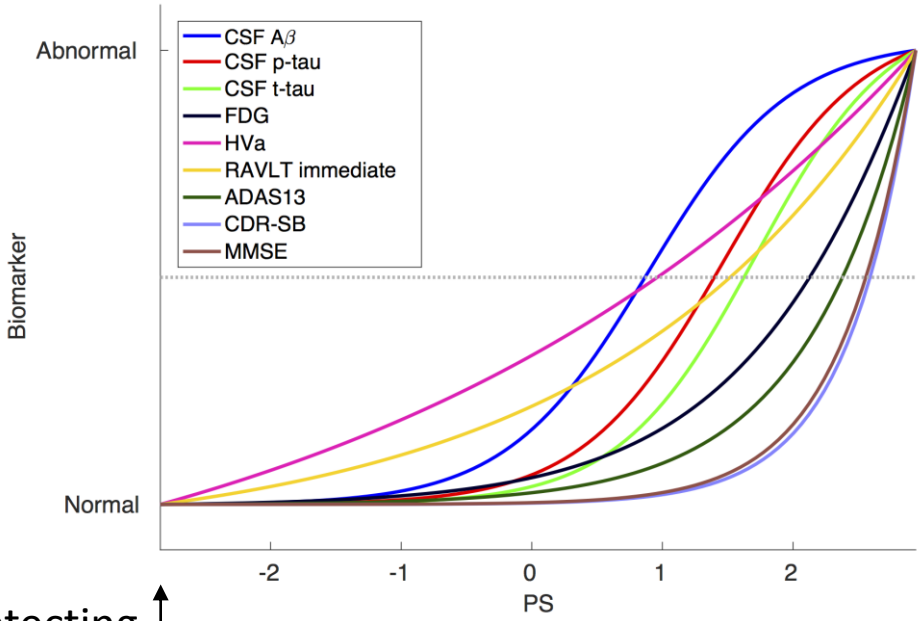
Model	N vs. MCI	MCI vs. AD	N vs. AD
p-tau, CDR, MMSE	1.5045	2.8606	4.2236
p-tau, ADAS13, CDR	1.0571	2.2485	3.7003
p-tau, ADAS13, MMSE	1.0140	2.2620	3.6831
RAVLT, ADAS13, MMSE	1.0129		
ADAS13, CDR, MMSE		2.1568	3.4584

b) Minimize error in individualized progression scores

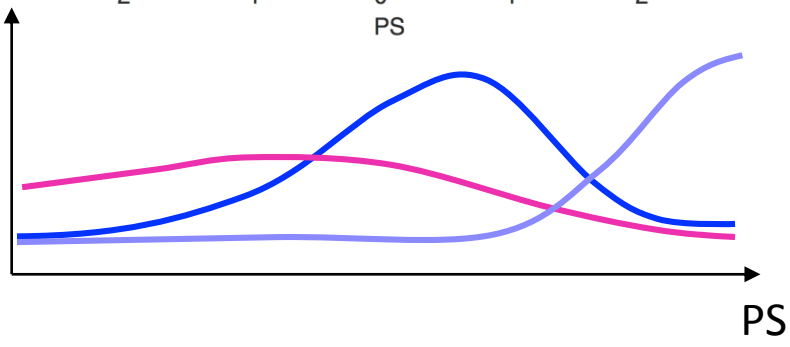
- Assuming model parameters are fixed, compute the variance of progression score at last visit
- Top four models:

Model	Individualized PS variance (median across individuals)
Aβ, t-tau, CDR	0.0593
Aβ, t-tau, FDG	0.0598
Aβ, t-tau, ADAS13	0.0612
Aβ, p-tau, t-tau	0.0659

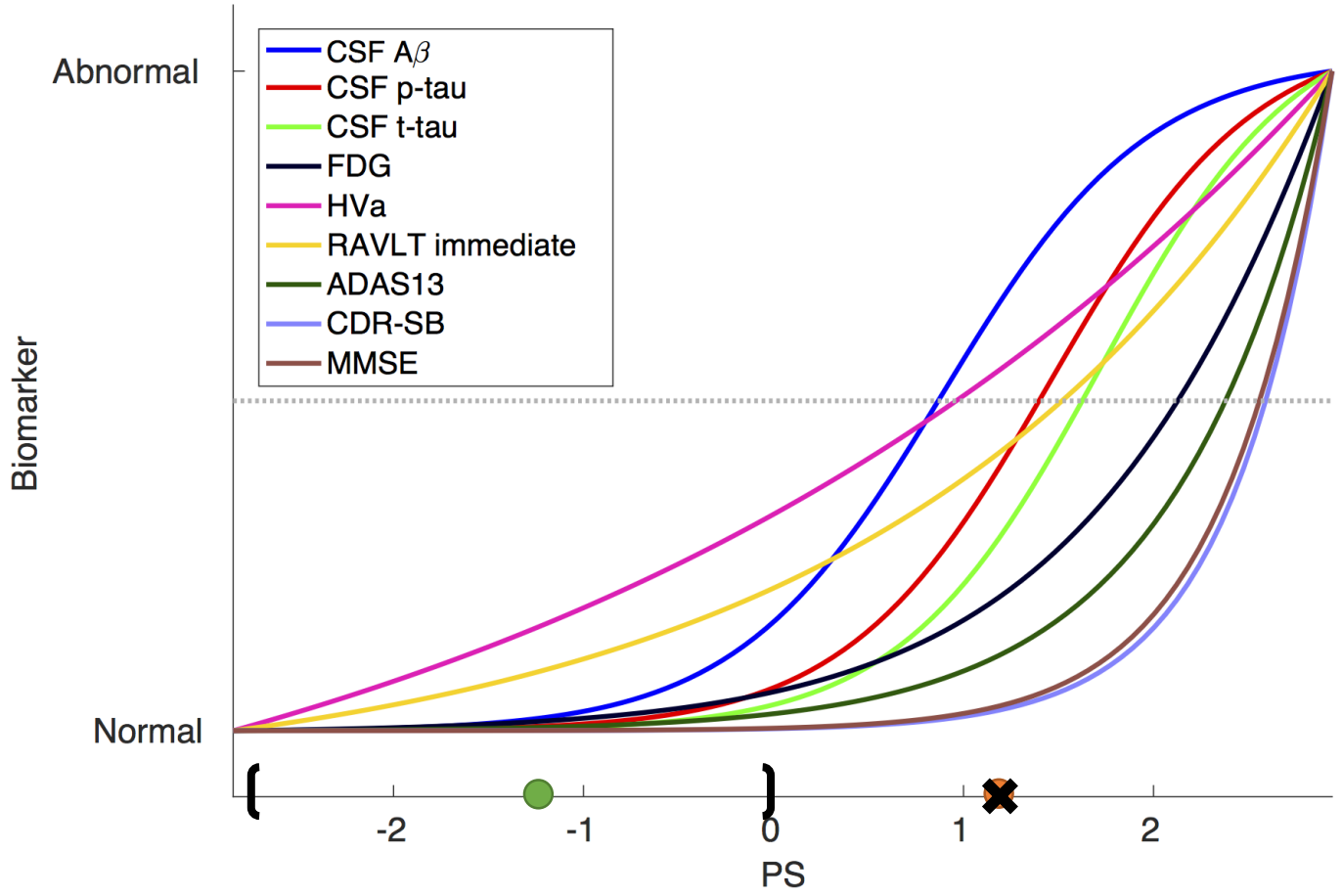
Optimality of outcome measures is dependent on disease stage



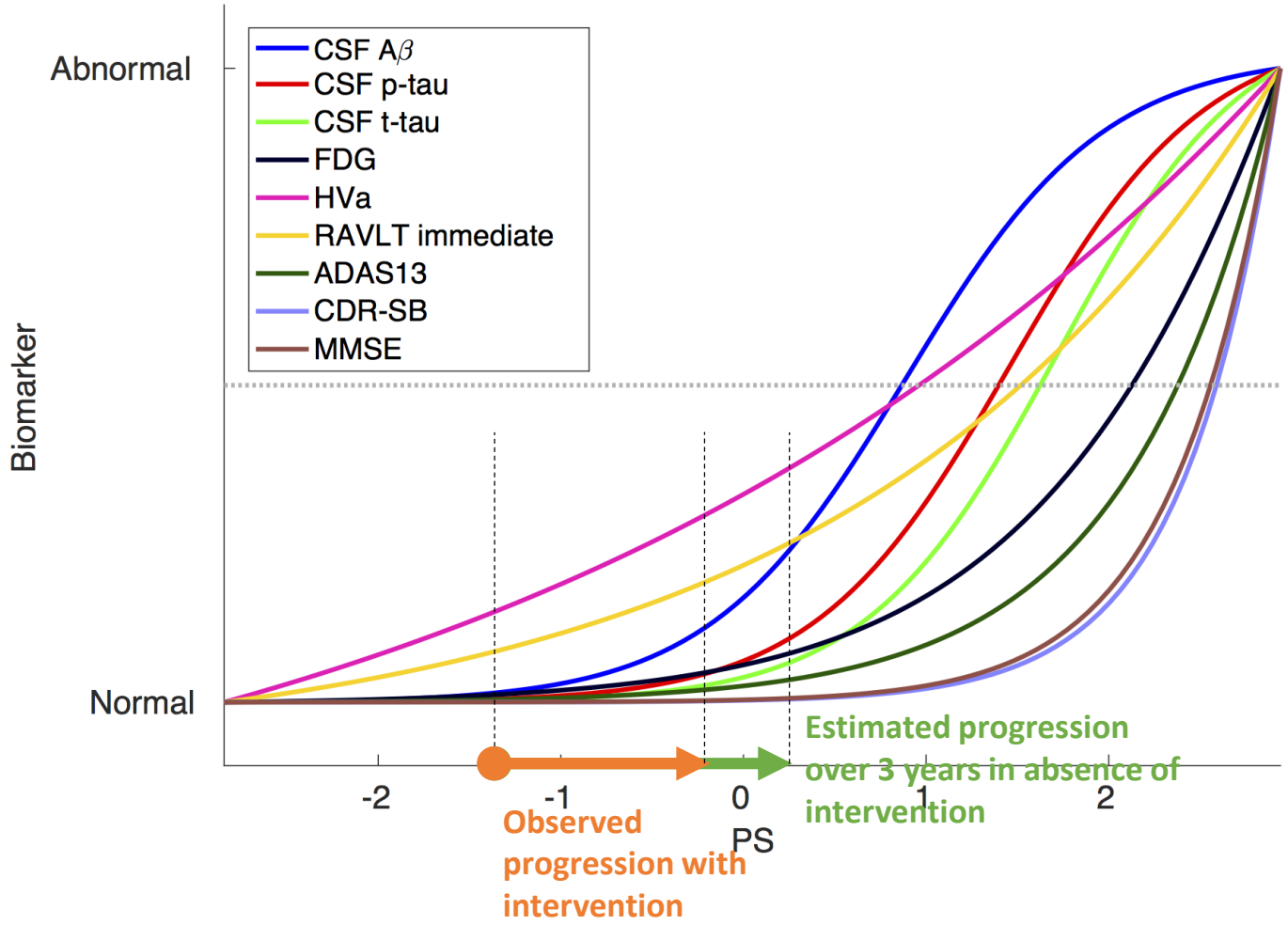
Sensitivity to detecting change in PS



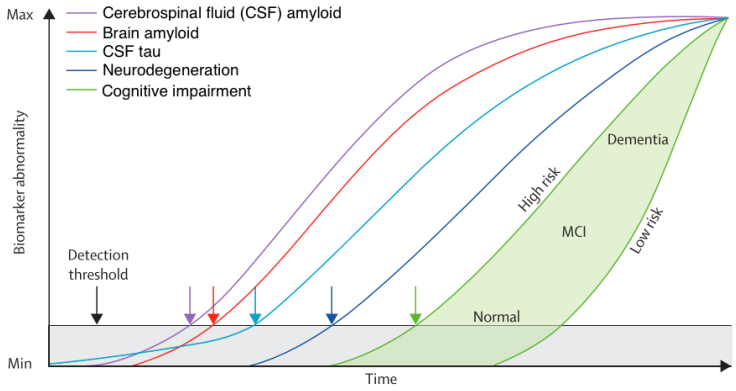
2. Recruitment of homogeneous samples



3. Individualized baselines against which to evaluate interventions



Conclusions



Progression score model enables:

- Multivariate analysis: *Characterize evolution of biomarkers*
  - Evaluation of scientific hypotheses about temporal dynamics of biomarkers
  - Selection of outcome measures for clinical trials
- Dimensionality reduction: *Progression Score is an individualized longitudinal composite*
  - Recruitment of homogeneous samples for clinical trials
  - Disease progression monitoring
- Individualized trajectory estimation
  - Baseline against which interventions can be evaluated

Collaborators

- Susan Resnick
- Yang An
- Luigi Ferrucci

- Sterling Johnson
- Rebecca Koscik

- Bruno Jedynak

- Jerry Prince
- Dean Wong