Biomarkers, Cognitive Reserve and Cognition in Alzheimer's Disease

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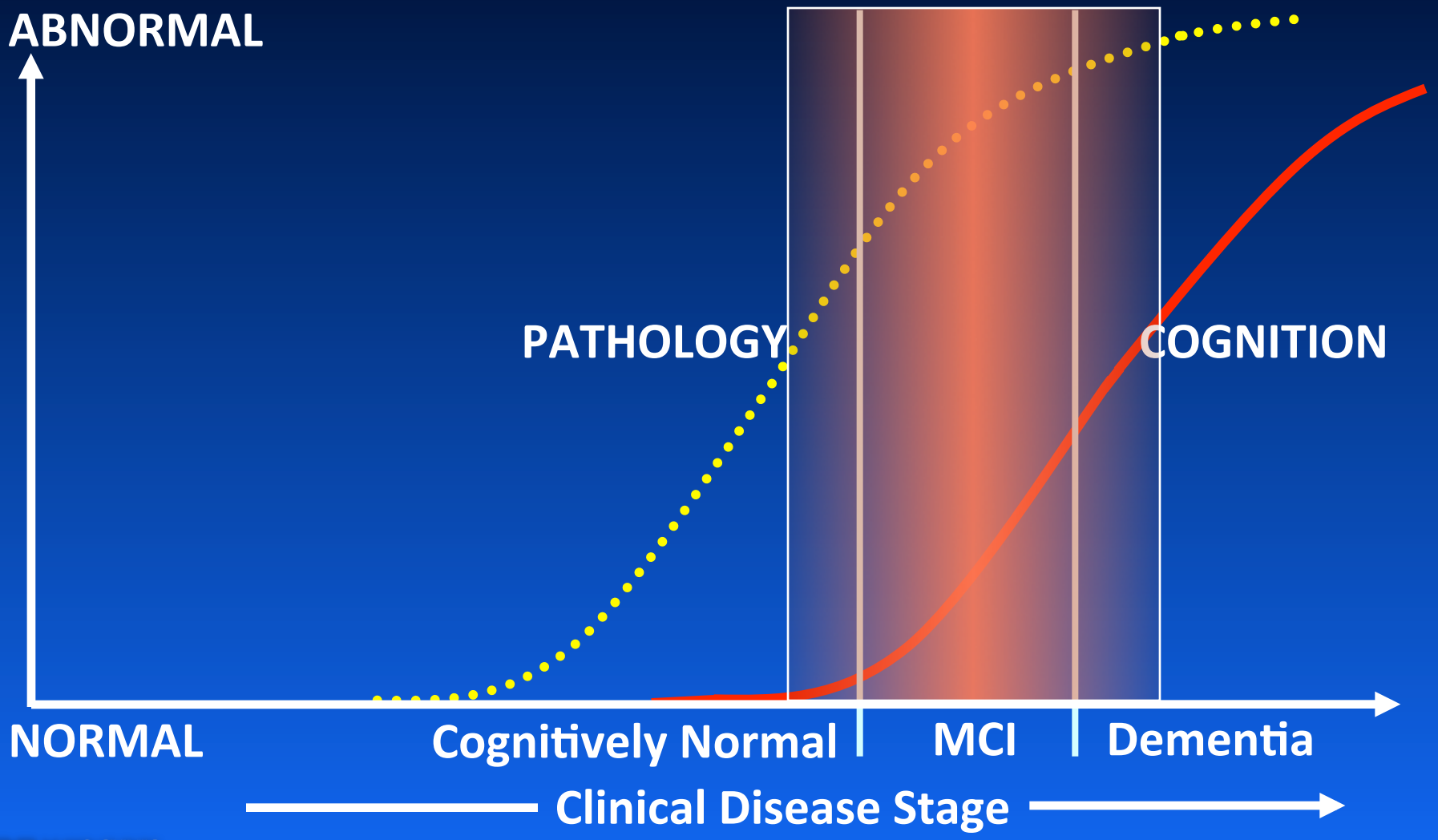
Pathological Cascade



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SURROGATE OF PATHOLOGY: BIOMARKERS

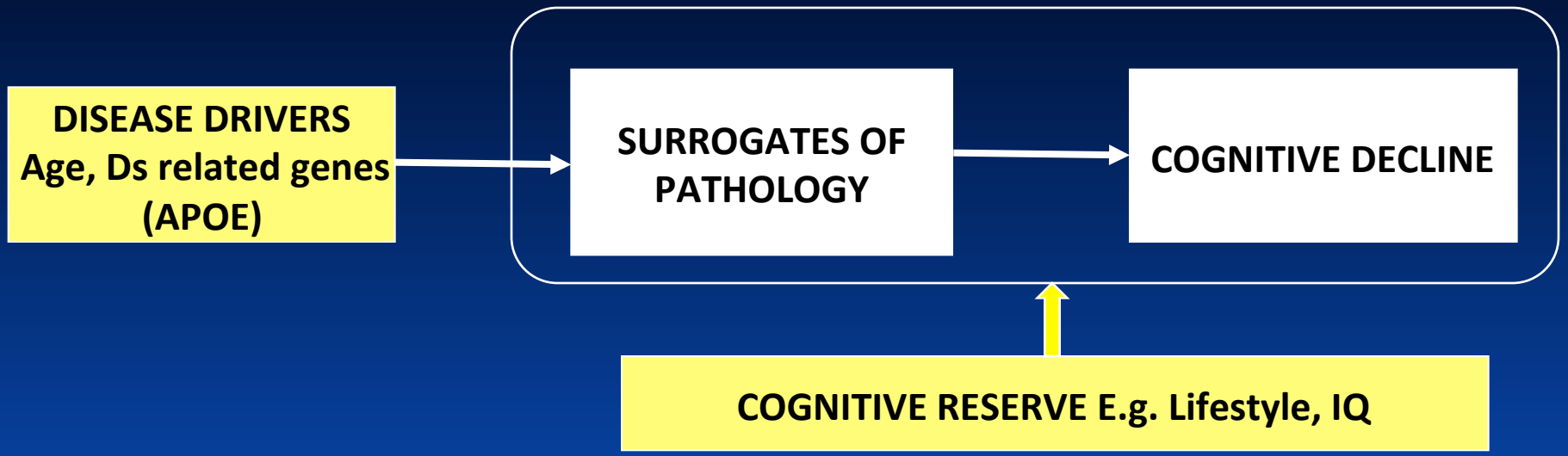
Biomarkers in AD
Considered for Clinical Trials and Observational Studies

- Brain Amyloid-osis
  - PIB-PET
  - CSF $A\beta_{1-42}$
- Neuronal Dysfunction and Tau mediated Injury
  - CSF t-tau
  - FDG-PET
- Neurodegeneration
  - Structural MRI – Hippocampal volume and STAND-scores

Role of Biomarkers in Alzheimer's Disease

- Diagnosis
- Prediction of Future Progression
- Evaluating Disease Progression
- Sample Selection and Enrichment
- Mechanistic Inferences about the disease process

Overview of the talk



- Biomarkers and Cognition in AD
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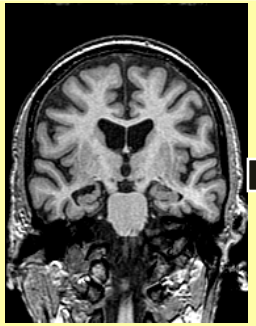
- Cognitive Reserve in AD

MRI Biomarker - STAND Scores

Automated Individual Patient Diagnosis

New Subject

MRI Scan

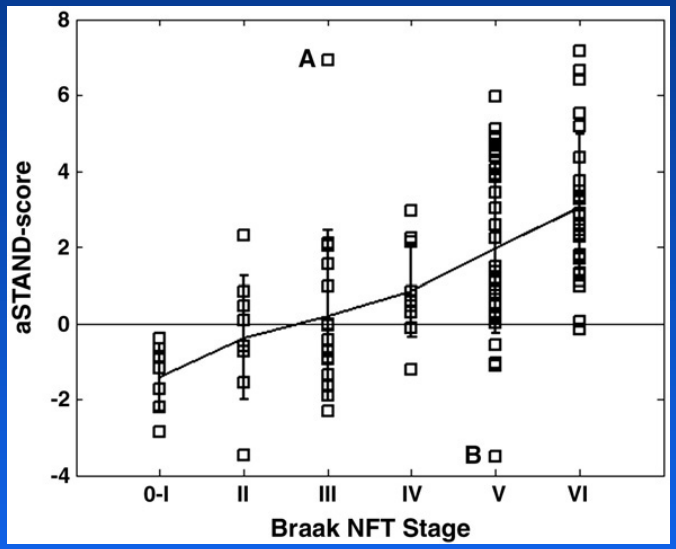


STAND Algorithm
(Library of AD and CN)

≥ 0 ABNORMAL

<0 NORMAL

- **Accuracy of the method in an independent sample ~ 90 %** (Vemuri et al. 2008a NeuroImage)
- **STAND-score correlates strongly with Braak NFT stages** (Vemuri et al. 2008b NeuroImage)



MRI and CSF in ADNI

Baseline CSF (t-tau, Aβ1-42) and MRI scans were obtained in 399 subjects (109 CN, 192 aMCI, 98 AD). We computed STAND-scores for these 399 subjects.

	STAND	t-tau	$A\beta_{1-42}$	t-tau/$A\beta_{1-42}$
AUROC	0.90	0.80	0.80	0.86
Threshold*	0.25	87 pg/mL	182 pg/mL	0.46
Sensitivity (%)	71	72	90	87
Specificity (%)	95	76	65	75
Test accuracy (%)	84	74	77	81

Vemuri et al. 2009a Neurology

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Predictors of Future Progression in AD

Table 4. Factors Influencing Rates of Progression

Predictor of Progression
Clinical severity
ApoE ε4 carrier status
Atrophy on MRI
^{18}FDG PET pattern of Alzheimer disease
CSF markers compatible with Alzheimer disease
Positive amyloid imaging scan

MRI: Jack et al. 1999, Visser et al. 1999 …….

FDG: Mosconi et al. 2004, Drzezga et al. 2005, Yuan Y et al. 2009

CSF: Hampel et al. 2003, Riemenschneider et al. 2005, Herukka et al. 2005

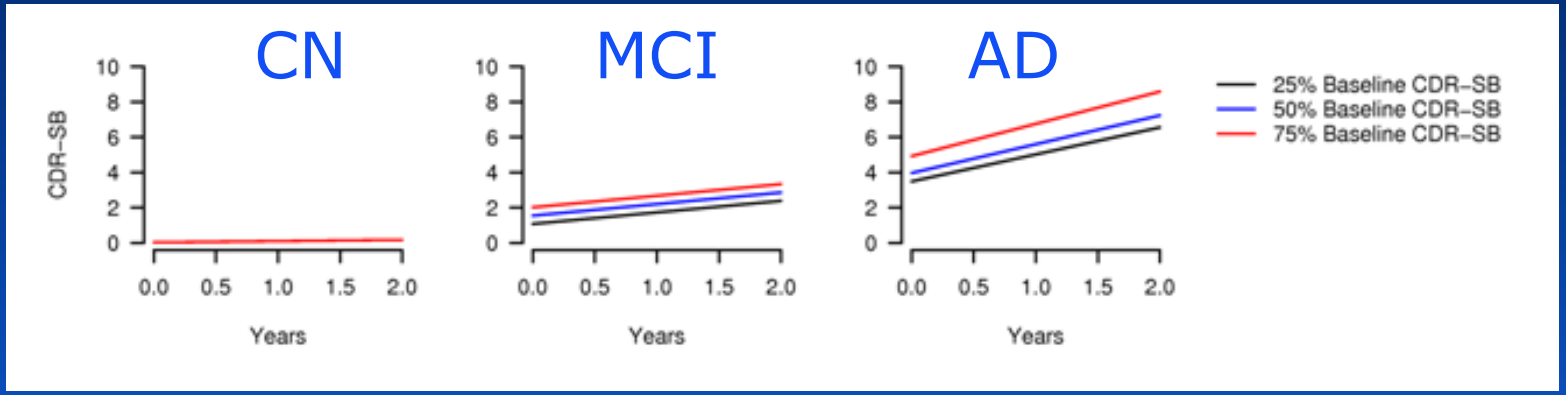
PIB: Okello et al. 2009, Morris et al. 2009

Petersen et al. 2009 Arch Neurology

Why biomarkers when clinical severity – predictive ?

Table 4. Factors Influencing Rates of Progression

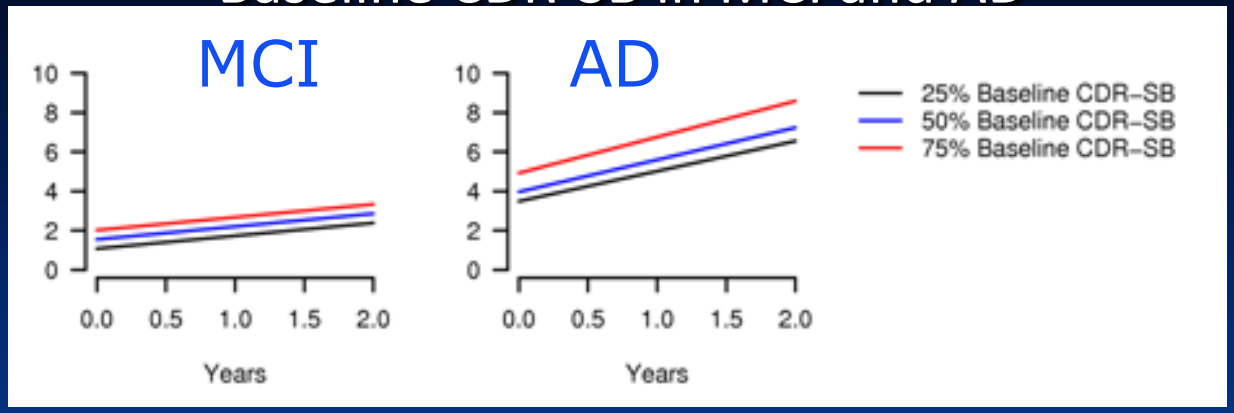
Predictor of Progression
Clinical severity



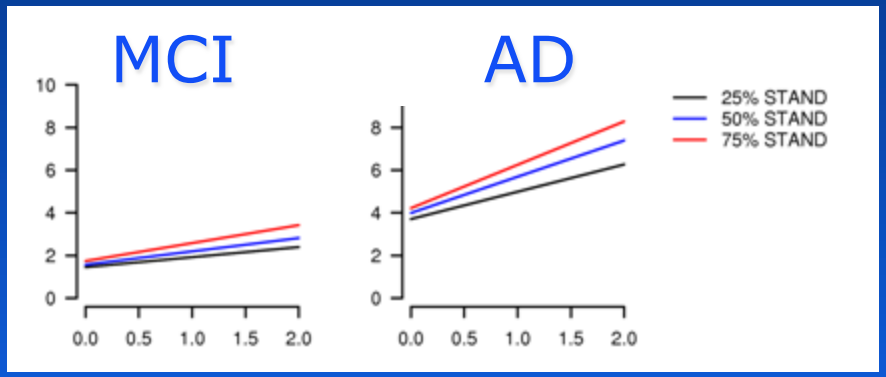
Average value of CDR-SB over 2-years by diagnosis group for the 25th, 50th, and 75th percentiles of baseline CDR-SB after accounting for baseline age

Value of MRI and CSF biomarkers ?

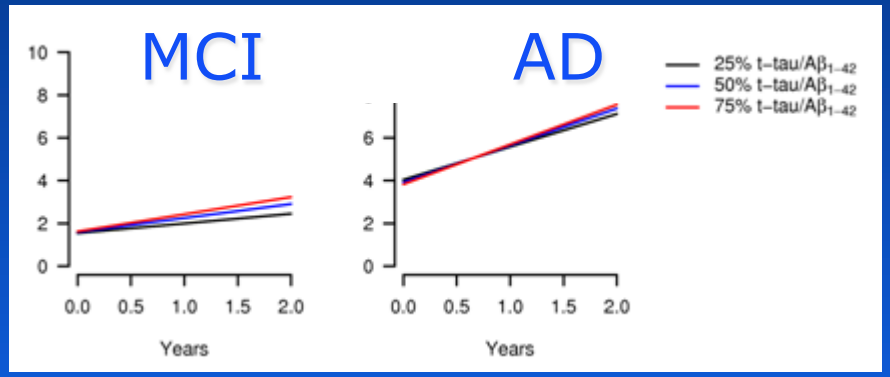
Baseline CDR-SB in MCI and AD



Baseline biomarkers predicting future cognitive decline in MCI – **after adjusting for baseline cognitive performance**



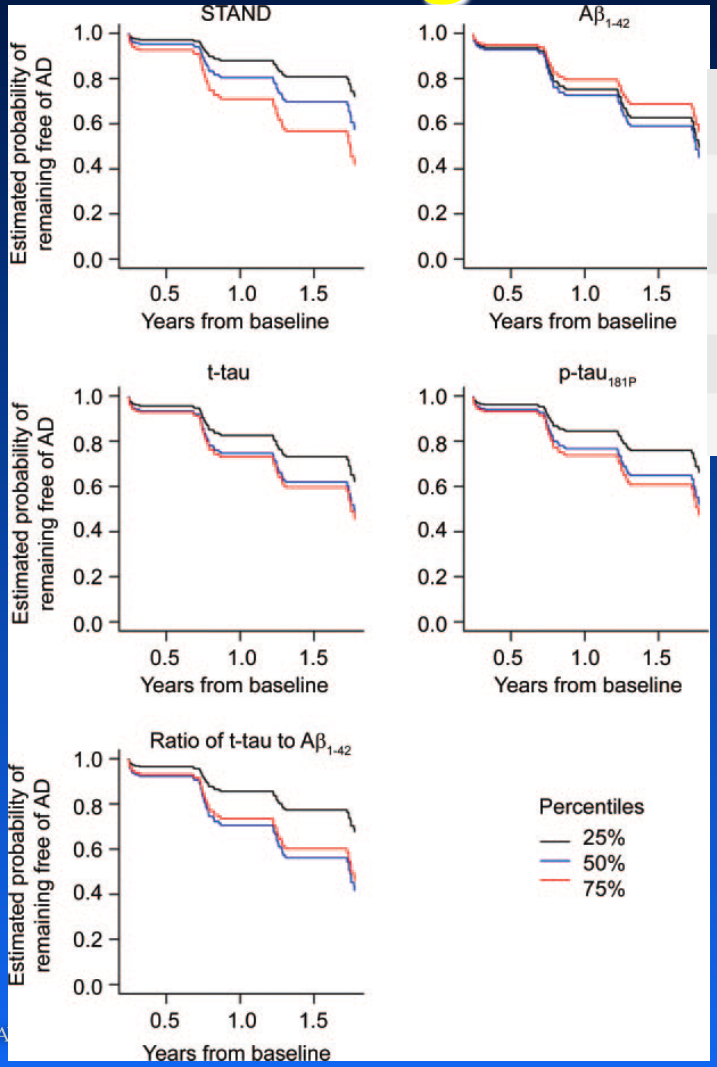
MRI – STAND



CSF t-tau/Aβ1-42 ratio

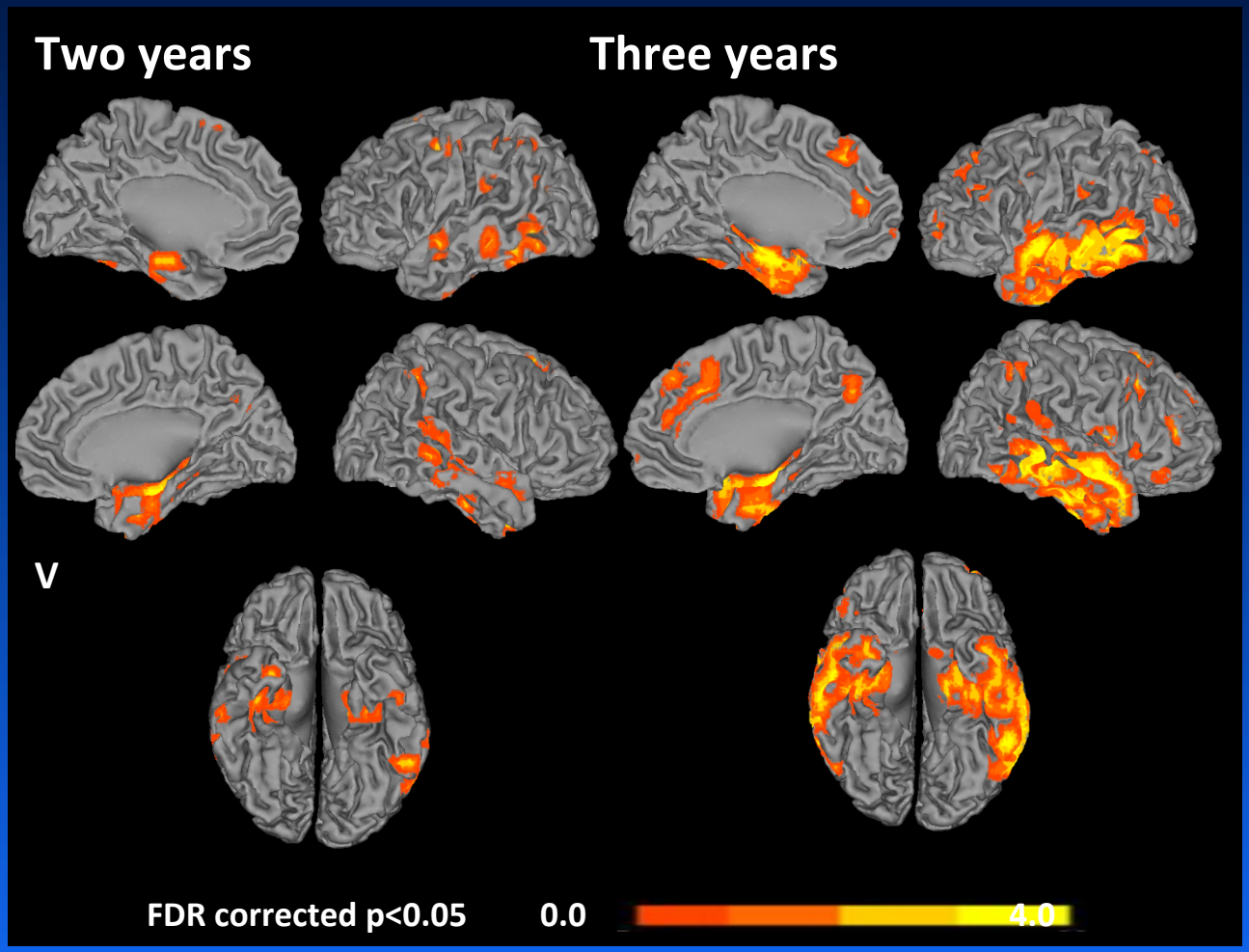
Vemuri et al. 2009b Neurology

Biomarker Prediction of Future Progression of MCI to AD



Biomarker	Model χ^2 (p)*	Nonlinearity χ^2 (p)†	Q3 vs Q1 HR (95% CI)‡
STAND score	19.0 (<0.001)	1.5 (0.22)	2.6 (1.7, 4.2)
$A\beta_{1-42}$	8.2 (0.02)	5.4 (0.02)	0.8 (0.5, 1.3)
log(t-tau)	6.8 (0.03)	5.0 (0.03)	1.7 (1.1, 2.6)
log($p\text{-tau}_{181P}$)	6.6 (0.04)	1.5 (0.22)	1.8 (1.1, 2.9)
log(t-tau/$A\beta_{1-42}$)	11.0 (0.004)	8.5 (0.004)	2.0 (1.1, 3.4)

Two Sample Pattern Differences: MCI Stables vs. Progressors



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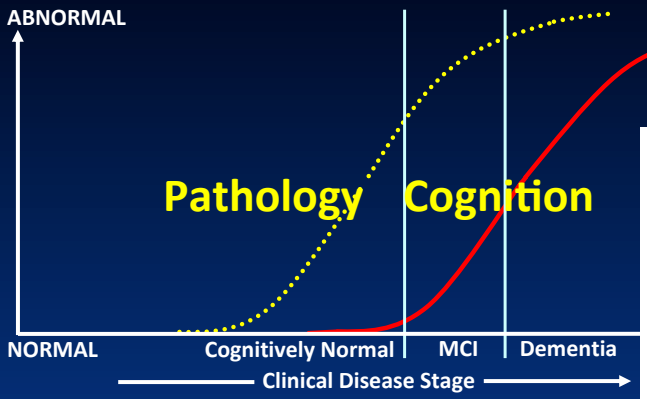
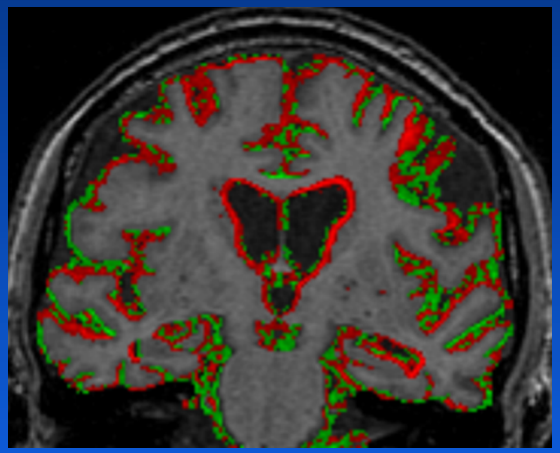
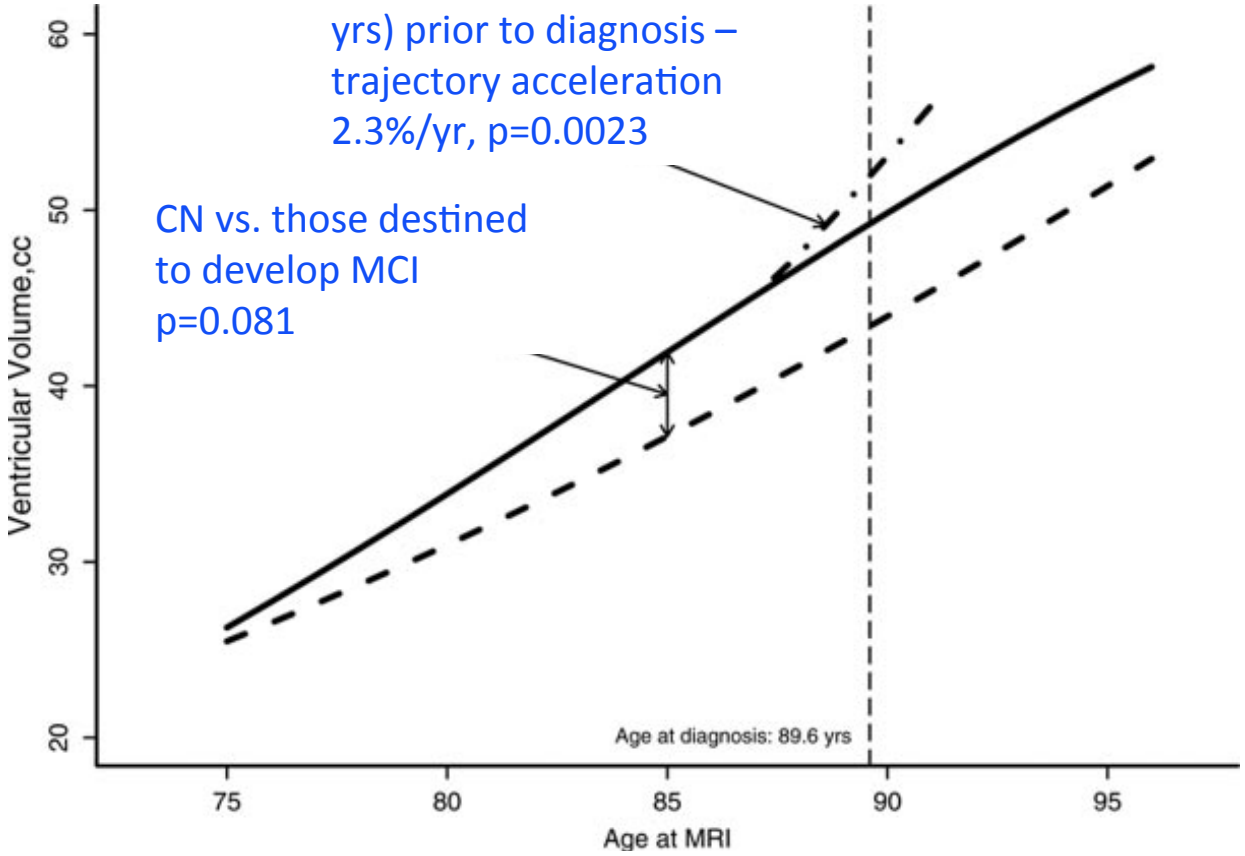
Disease Progression: Pathology





2.3 yrs (95% CI 0.3-5.6 yrs) prior to diagnosis – trajectory acceleration 2.3%/yr, p=0.0023

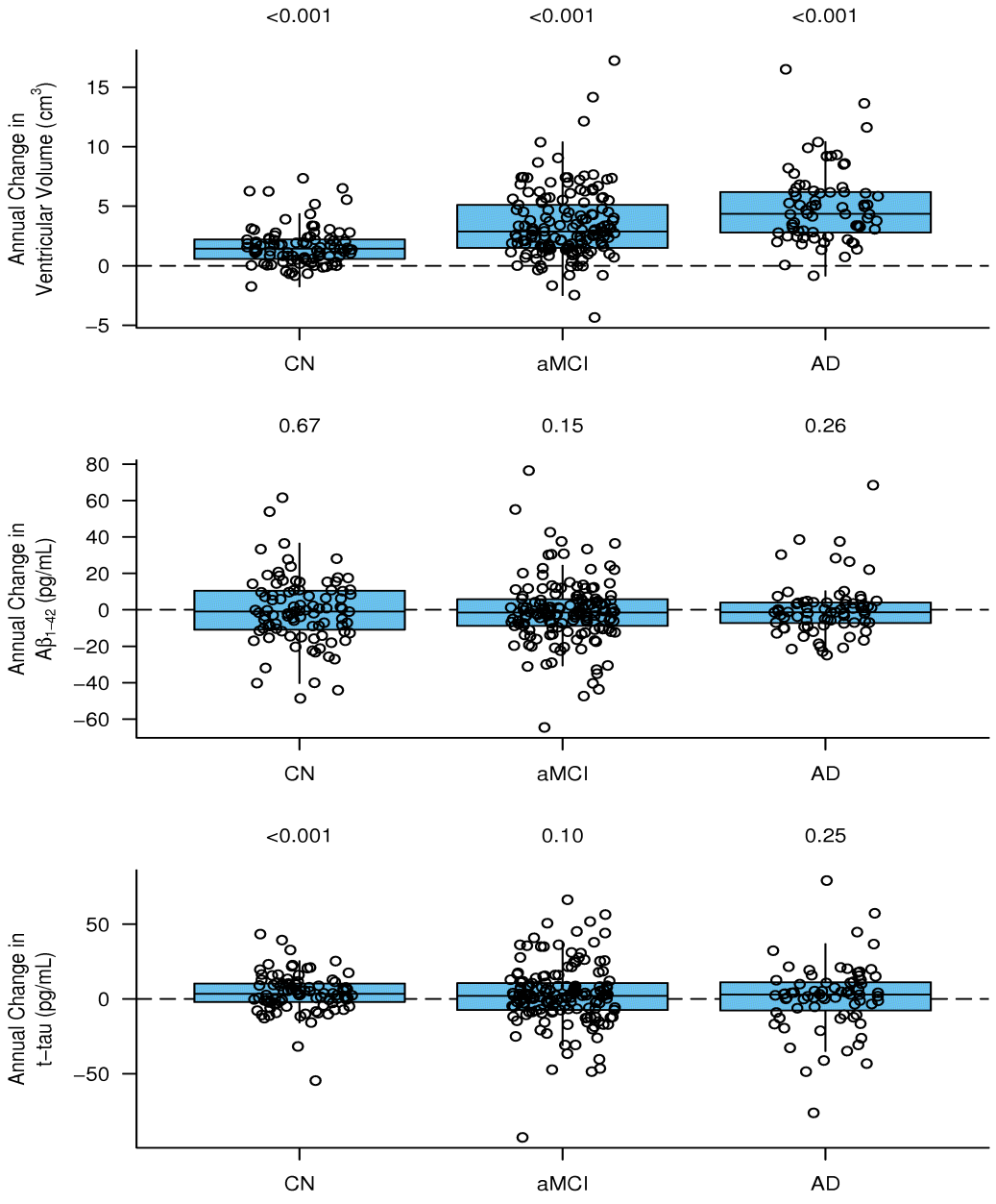
CN vs. those destined to develop MCI p=0.081



Carlson et al. 2008 Neurology

Disease Progression: MRI and CSF

- ADNI sample
  - Baseline and 12-month CSF (t-tau, $A\beta_{1-42}$) and MRI in 312 subjects (92 CN, 149 aMCI, 71 AD).
- Significant annual change in MRI which differed by clinical group.



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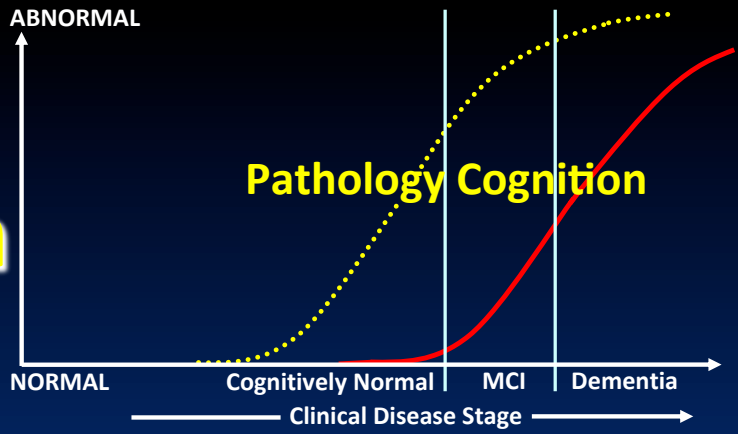
Vemuri et al. 2010 *Neurology*

Disease Progression: Correlation with Cognition



Spearman rank-order correlations (and p-values)

Annual Change	All (n=312)	CN (n=92)	aMCI (n=149)	AD (n=71)
Annual change vent. vol.				
MMSE	-0.33 (<0.001)	-0.19 (0.07)	-0.29 (<0.001)	-0.31 (0.01)
CDR-SB	0.37 (<0.001)	0.09 (0.4)	0.30 (<0.001)	0.38 (0)
Annual change $A\beta_{1-42}$				
MMSE	0.14 (0.02)	0.20 (0.06)	0.05 (0.55)	0.30 (0.01)
CDR-SB	-0.05 (0.36)	-0.02 (0.87)	-0.05 (0.51)	-0.11 (0.34)
Annual change t-tau				
MMSE	0.11 (0.05)	0.12 (0.25)	0.10 (0.22)	0.06 (0.6)
CDR-SB	-0.05 (0.4)	-0.02 (0.83)	-0.04 (0.64)	-0.03 (0.81)

Vemuri et al. 2010 Neurology

Efficacy of Therapeutics: Required Sample Size

Estimated sample size required to detect a 25% improvement in annualized change in cognitive status or biomarkers with 80% power (α=0.05) in aMCI and AD

Variable	aMCI (N)	AD (N)
MMSE	1963	766
CDR-SB	604	445
ADAS-Cog	2543	510
Vent Vol	186	100
$A\beta_{1\text{-}42}$	>10 K	>10 K
t-tau	>10 K	>10 K
t-tau/ $A\beta_{1\text{-}42}$	>10 K	>10 K

Vemuri et al. 2010 *Neurology*

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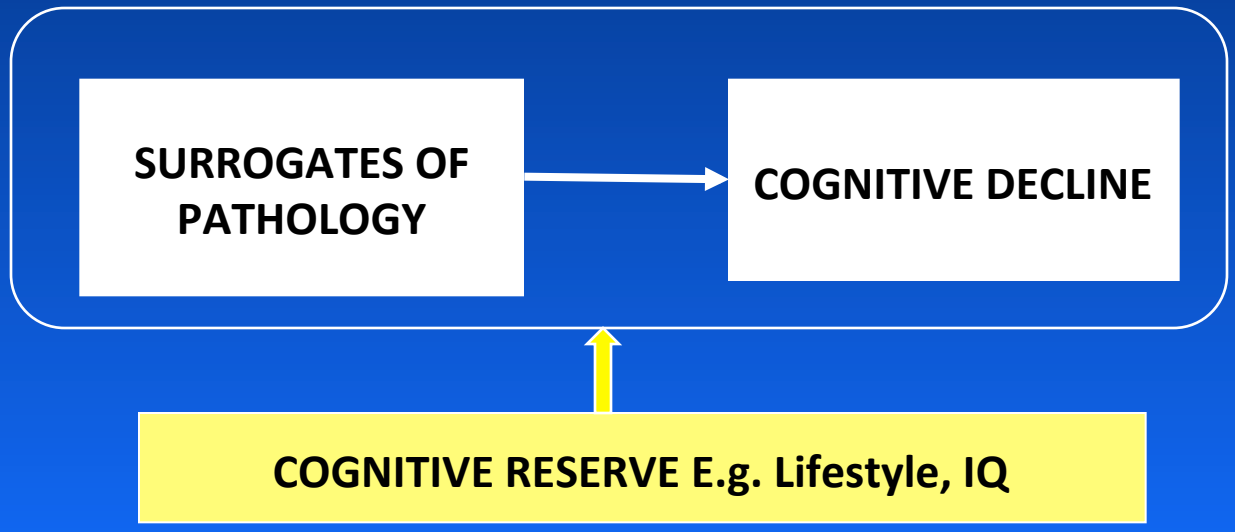
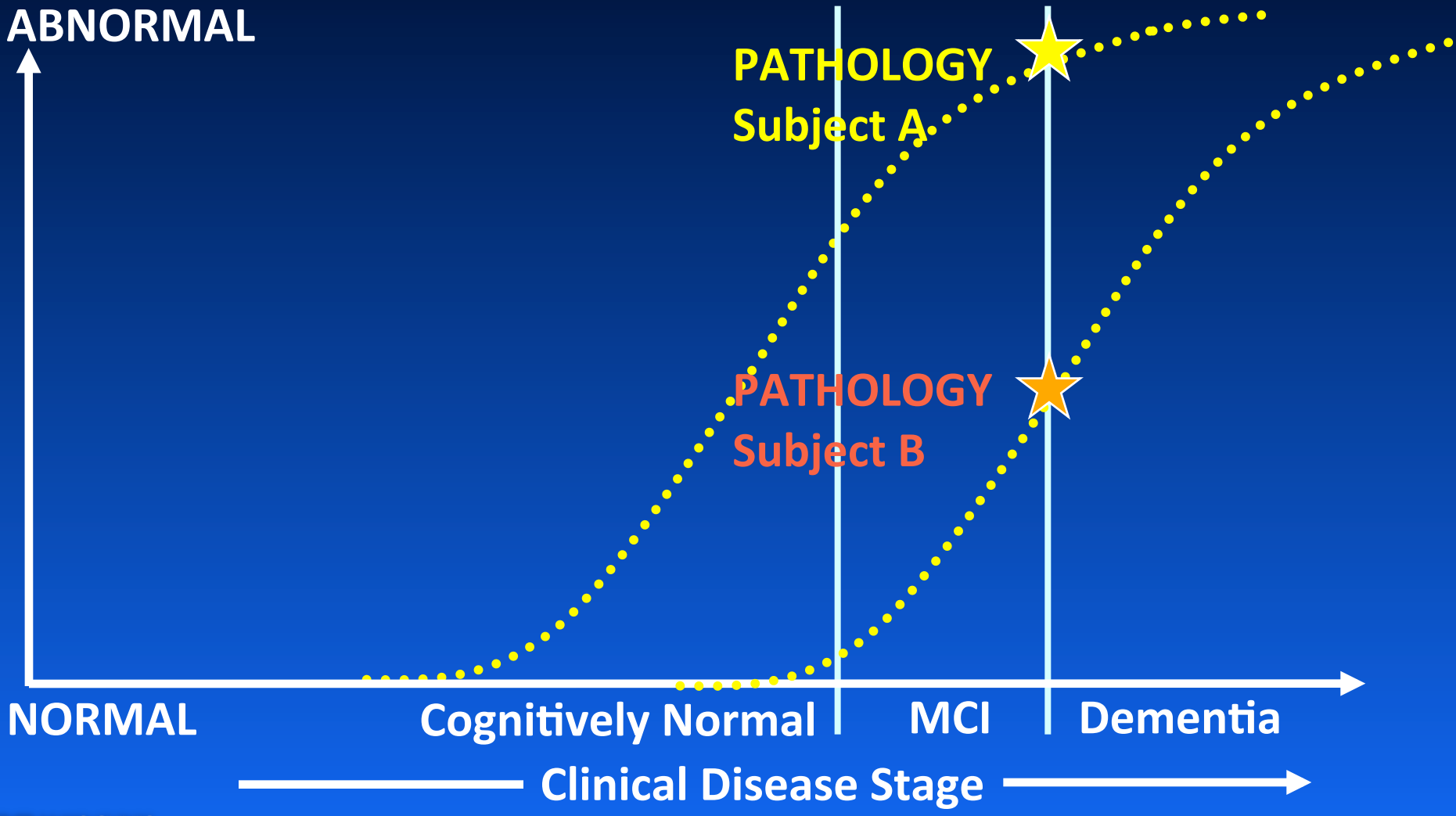


Degrees of Pathology for Clinical Expression of Disease



Why do some subjects with AD pathology remain cognitively normal during life while some others develop dementia?

COGNITIVE RESERVE

IQ, Education, Physical activities and Cognitive activities

Two different studies:

ADNI (CN, MCI and AD)

Mayo Clinic Study of Aging (Non demented population based sample)

Mayo Clinic Study of Aging

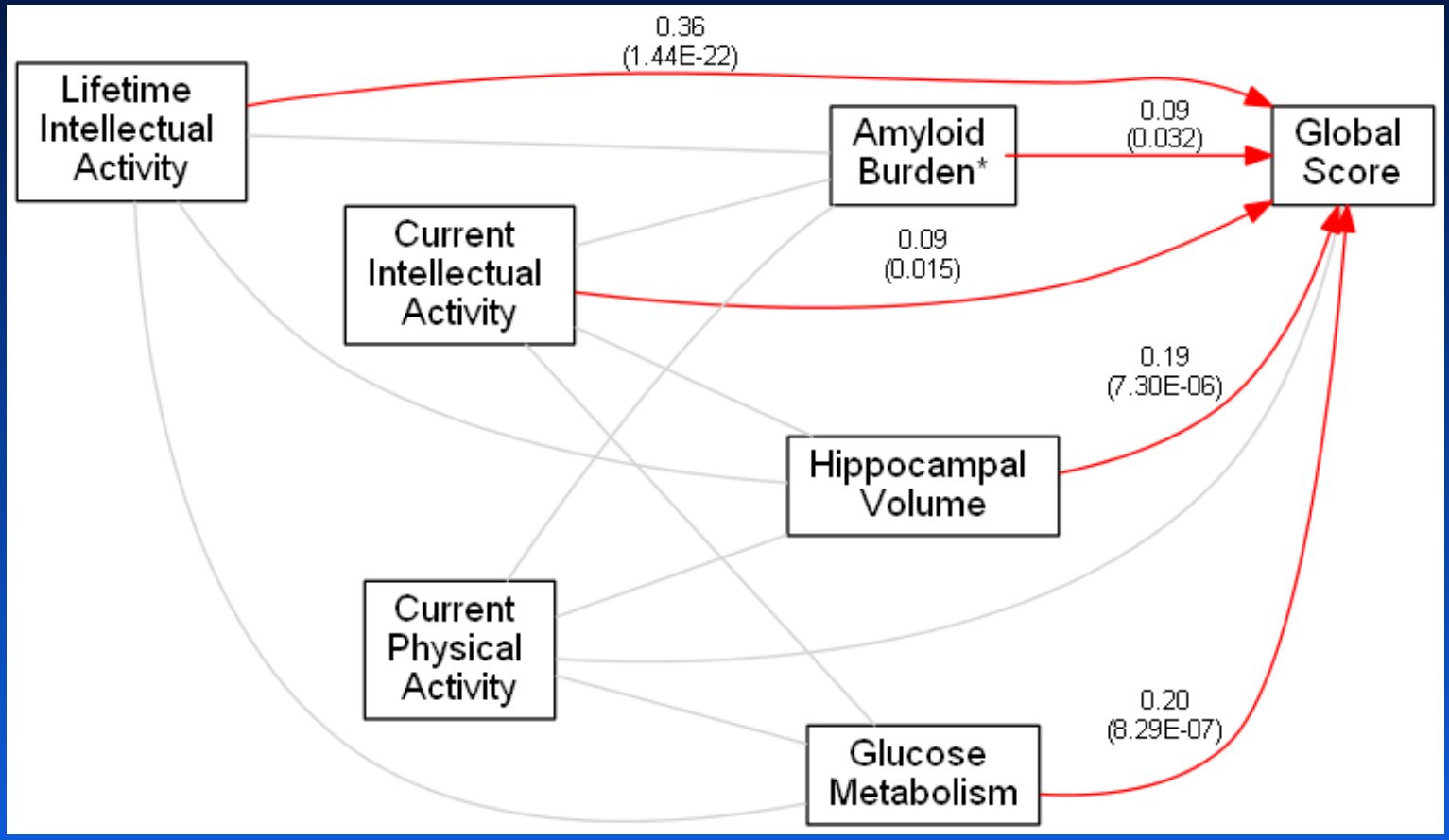
Biomarkers: MRI, PIB, FDG; Reserve: Lifestyle

515 non-demented population based elderly

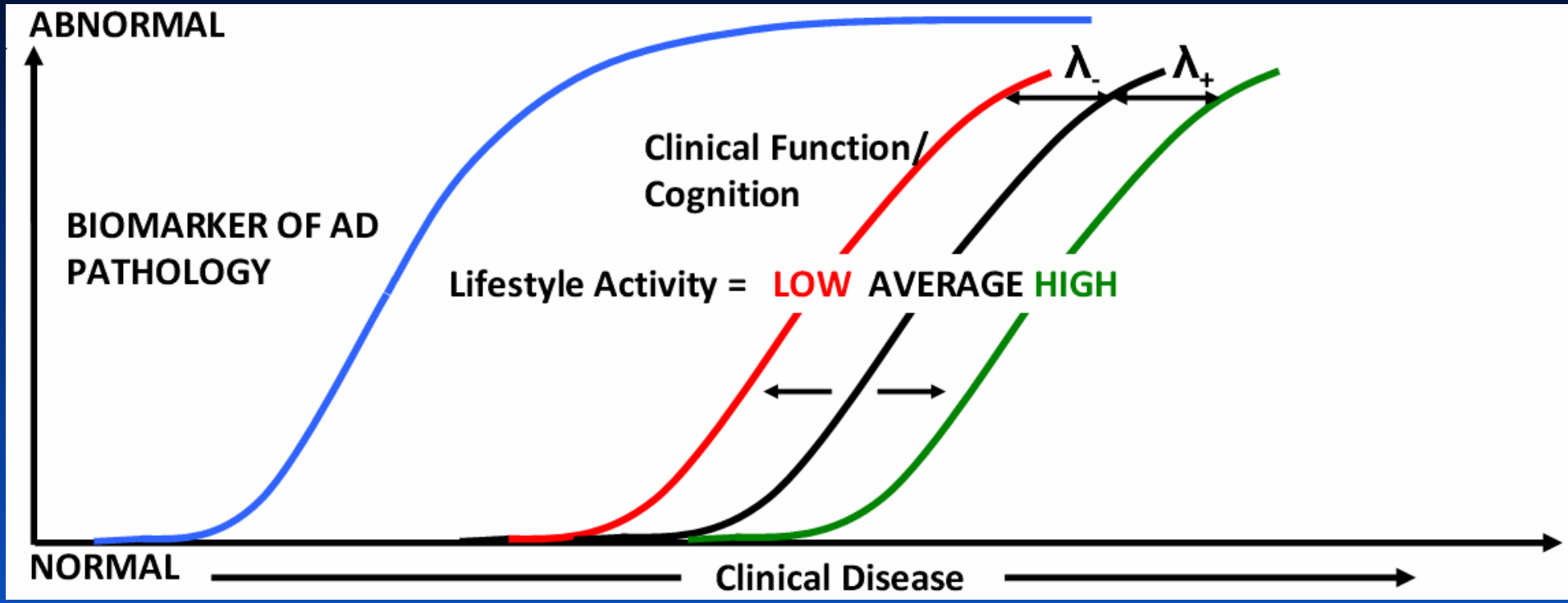
- Intellectual Lifestyle – Current and Lifetime
  - Education
  - Job Score
  - Current Intellectual Activity
- Physical Activity Lifestyle
  - Current Physical Activity

Vemuri et al. 2012 Annals of Neurology

Path Analysis



Model summarizing the data



λ for Lifetime intellectual activity >> Current intellectual activity

λ for physical activity ~= 0

Where are we ?

- Different biomarkers to measure different aspects of the pathology.
- Biomarkers provide information regarding disease progression (in addition to the clinical information).
- Neurodegeneration (MRI) become abnormal later and closely correlates with cognition – disease progression.
- Studies provide evidence that cognitive reserve (lifestyle variables and IQ) may delay the onset of dementia but do not significantly influence the expression of AD pathophysiology.

Future Directions and Considerations

- Longitudinal studies and statistical methods to map the local and global dynamic progression of the disease.
- Account for individual differences in Alzheimer's disease risk modifiers.
- Efficiently apply these disease models for patient care.

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