CLINICAL WORK-UP FOR PATIENTS WITH SUSPECTED DEMENTIA

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Disclosure

- Scientific advisory board for NeuroPhage
- Consultant to Elan Corporation, Wyeth, Eisai Inc., Bristol-Myers Squibb, Eli Lilly and Company, NeuroPhage, Merck & Co., Roche, Amgen, Abbott, Pfizer Inc, Novartis, Bayer, Astellas, Dainippon, Biomarin, Solvay, Otsuka, Daiichi, AstraZeneca, Janssen, Medivation, Inc., Theravance, Cardeus, Anavex and Kyowa Hakko Kirin Pharma
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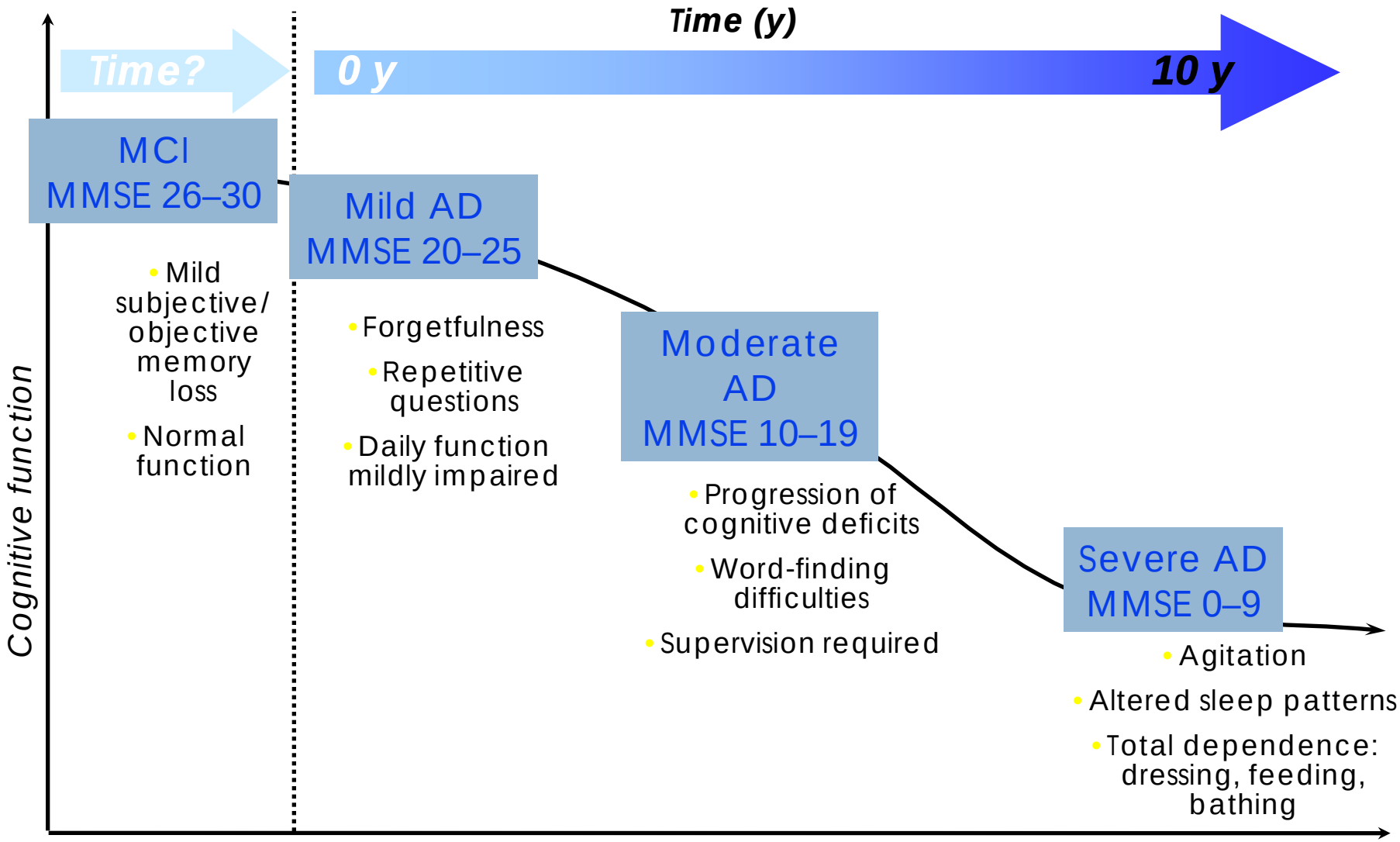
Very brief background

- Dementia is syndrome: cognitive impairment causing functional decline
- Most age-related dementia is AD
- Differential dx includes vascular dementia, fronto-temporal dementia, Lewy body disease, B12 deficiency, hypothyroidism, depression …
- Dementia in the US is an exploding epidemic; baby boomers have reached the age of risk

Clinical Progression of AD and MCI



Clinical evaluation of dementia

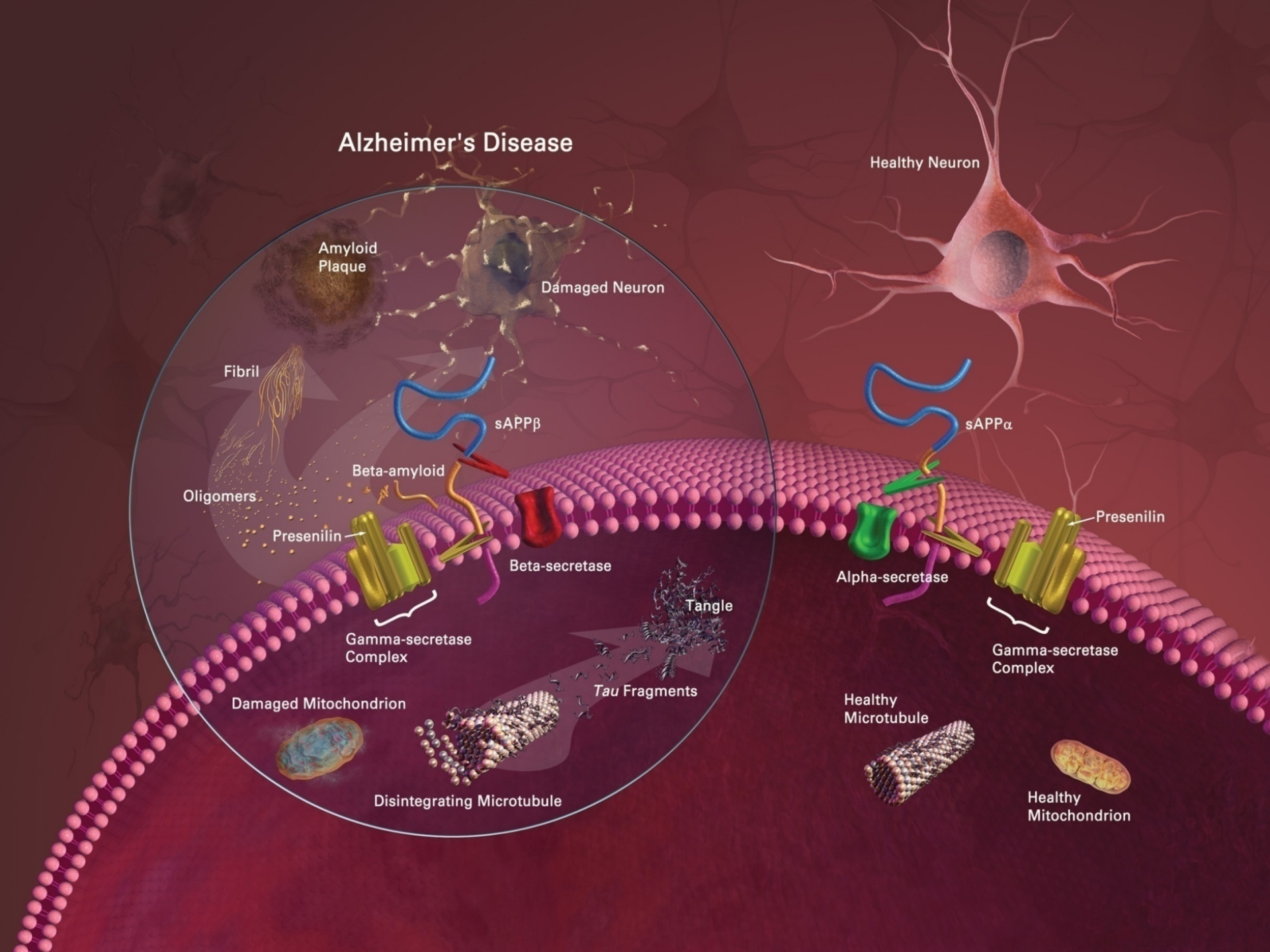
- **Detailed interview with patient and family**
  - **Cognitive/behavioral symptoms**
  - **Impact on function (work, community, driving, finances, social activity, judgment)**
  - **Mental status examination**
- B12, TSH
- Neuropsych testing?
- Structural Imaging?
- APOE genotyping?
- Spinal tap?
- FDG-PET?

Diagnostic challenges

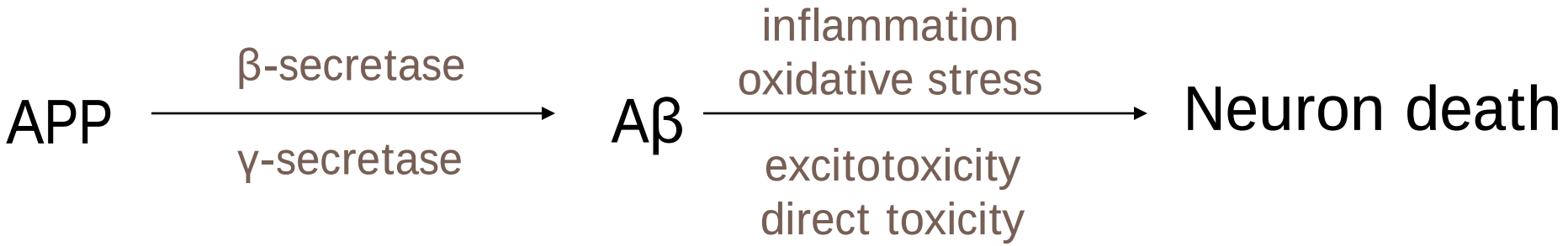
- Atypical presentation
  - absence of predominant episodic memory impairment
  - predominant depression or behavioral symptoms
  - early age of onset
  - atypical time course
  - insufficient history from informant
  - Comorbidities that might contribute to cognitive impairment

Pathology of AD

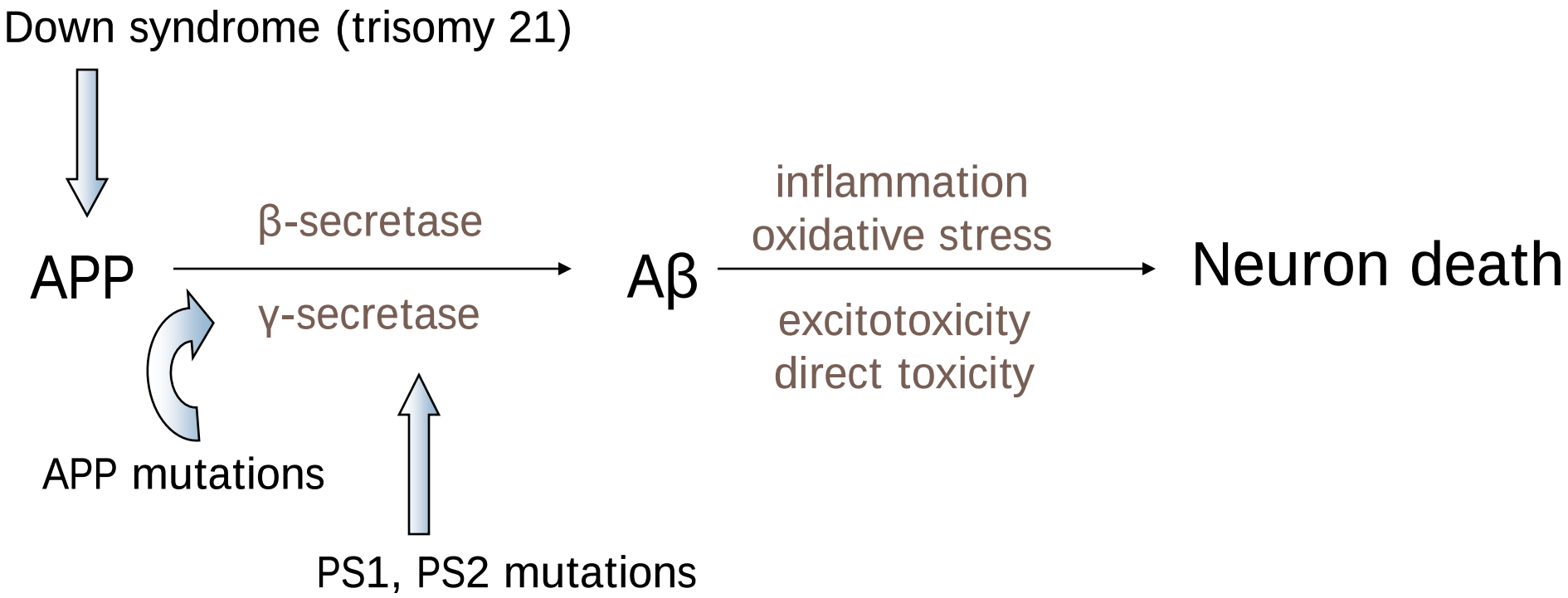
- Amyloid plaques and neurofibrillary tangles (plus synaptic loss, neuron loss, atrophy, gliosis …)
- Cannot diagnose AD without amyloid
- New guidelines (2011): disentangled from clinical diagnosis of dementia


Alzheimer's Disease
Amyloid Plaque
Damaged Neuron
Fibril
sAPPβ
Beta-amyloid
Oligomers
Presenilin
Beta-secretase
Gamma-secretase Complex
Tangle
Tau Fragments
Damaged Mitochondrion
Disintegrating Microtubule
Healthy Neuron
sAPPα
Alpha-secretase
Presenilin
Gamma-secretase Complex
Healthy Microtubule
Healthy Mitochondrion

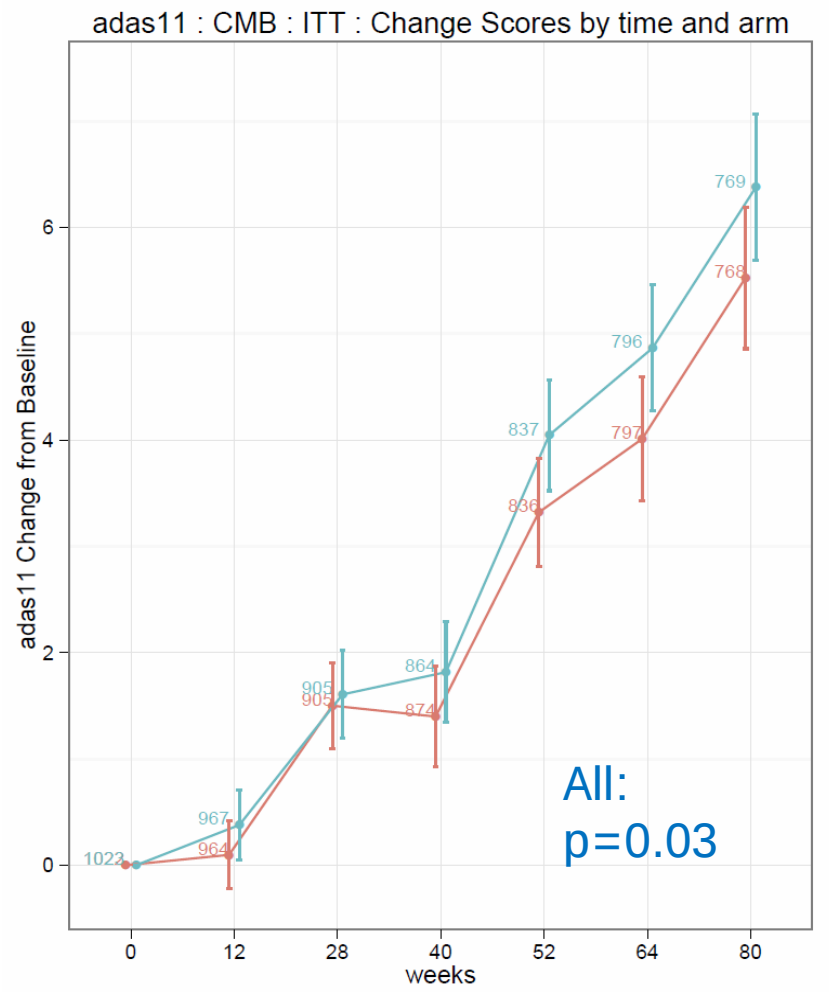
Pivotal pathway in AD pathophysiology

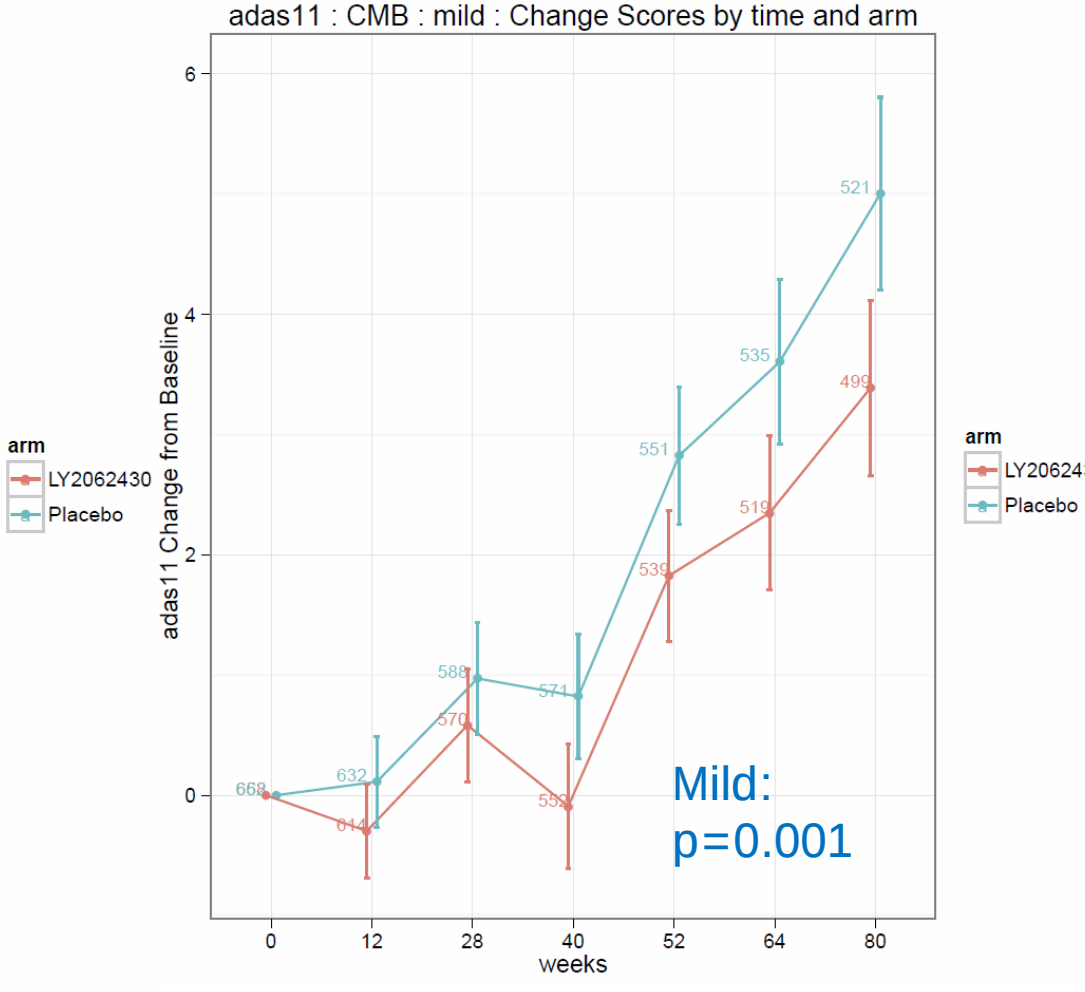


Genetic causes of AD

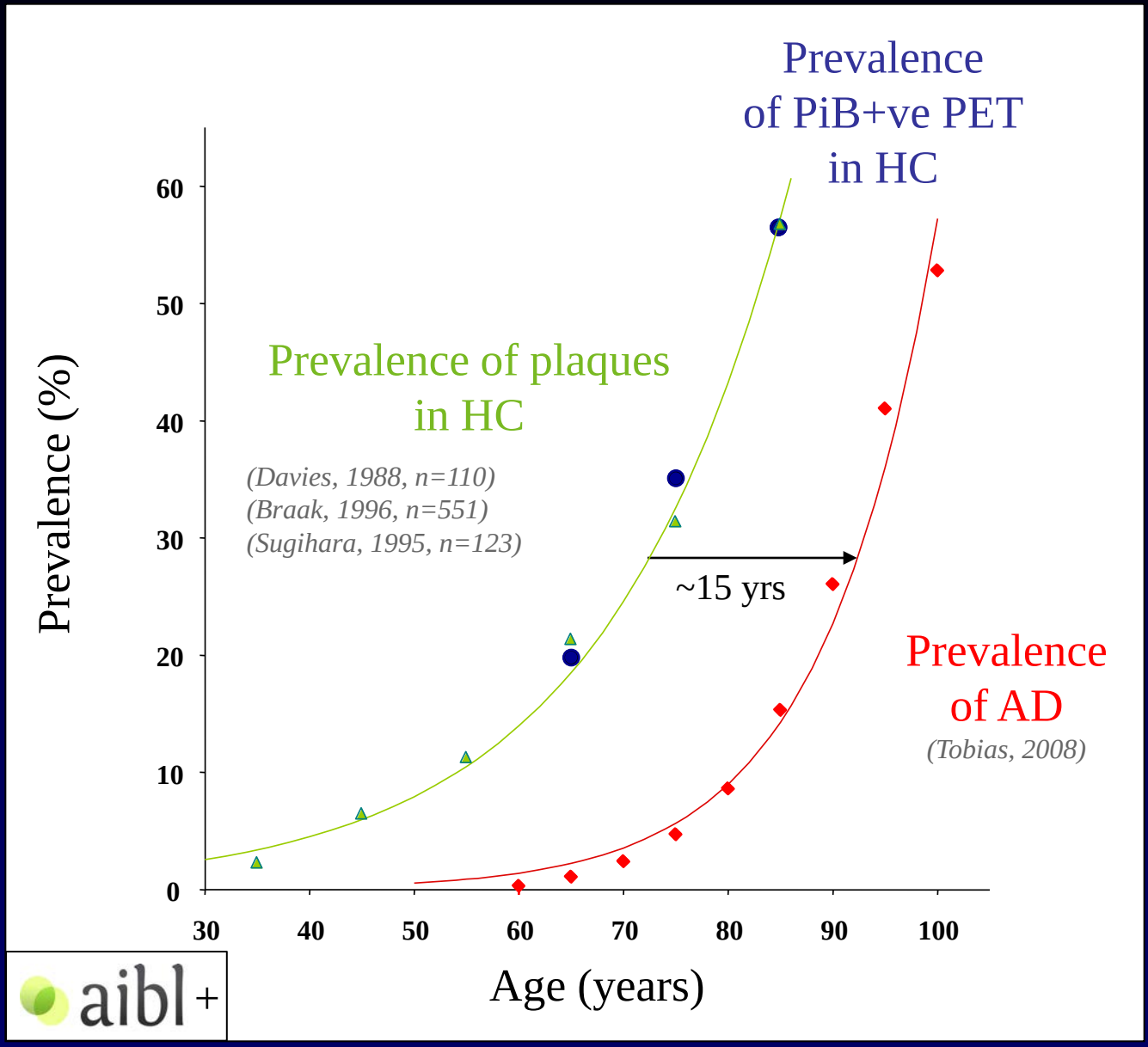


Solanezumab ADAScog11- pooled



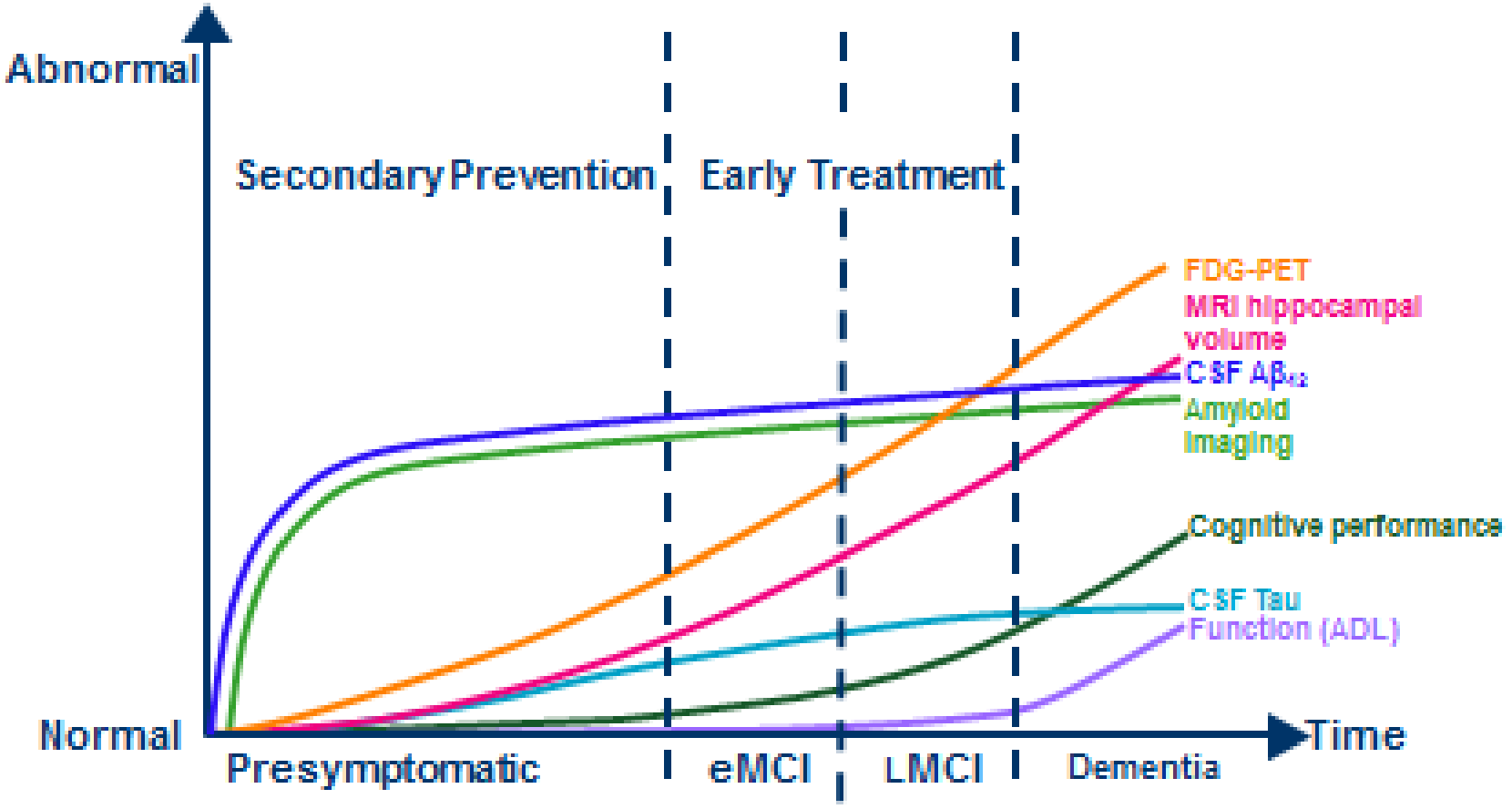


Preclinical Alzheimer's Disease?



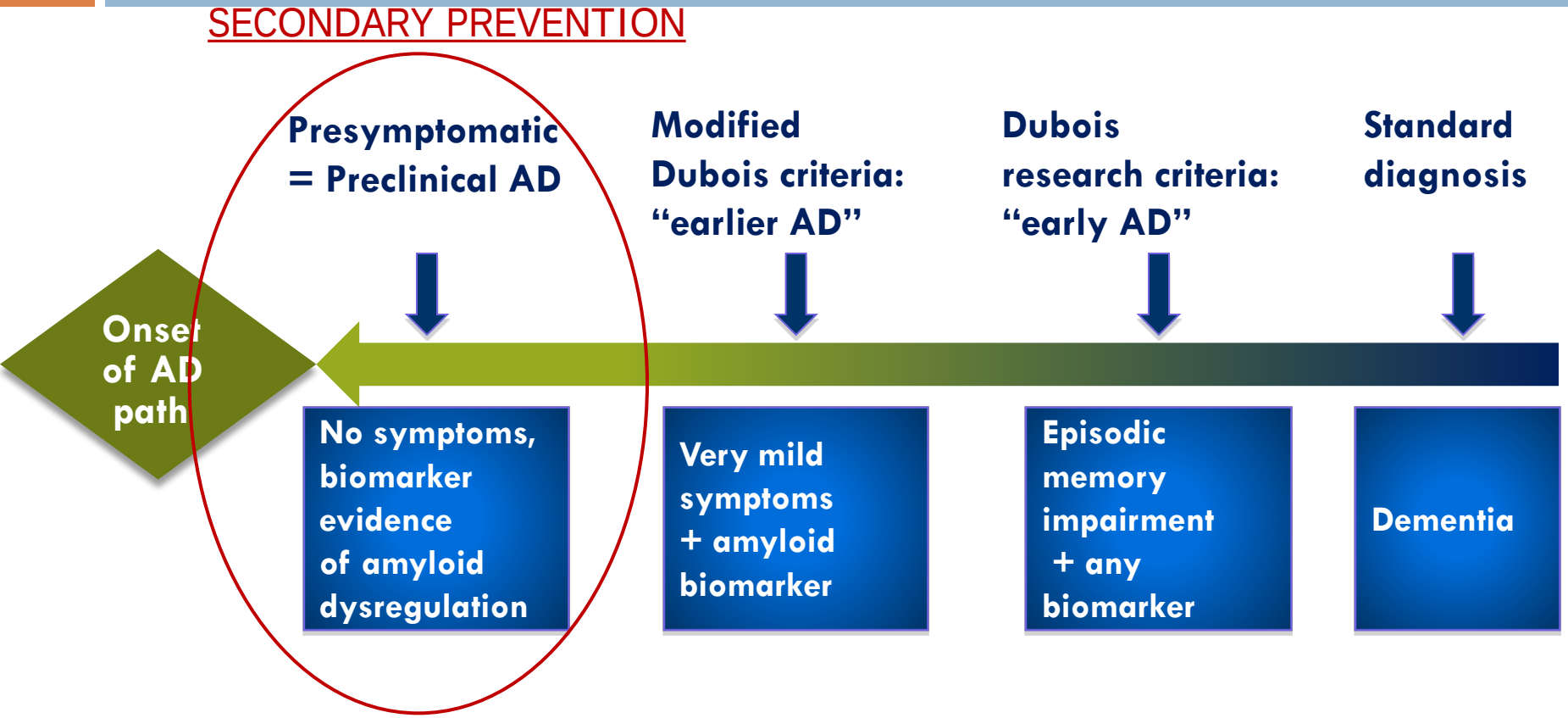
Rowe C et al *Neurobiology of Aging* 2010

AD Progression: ADNI model



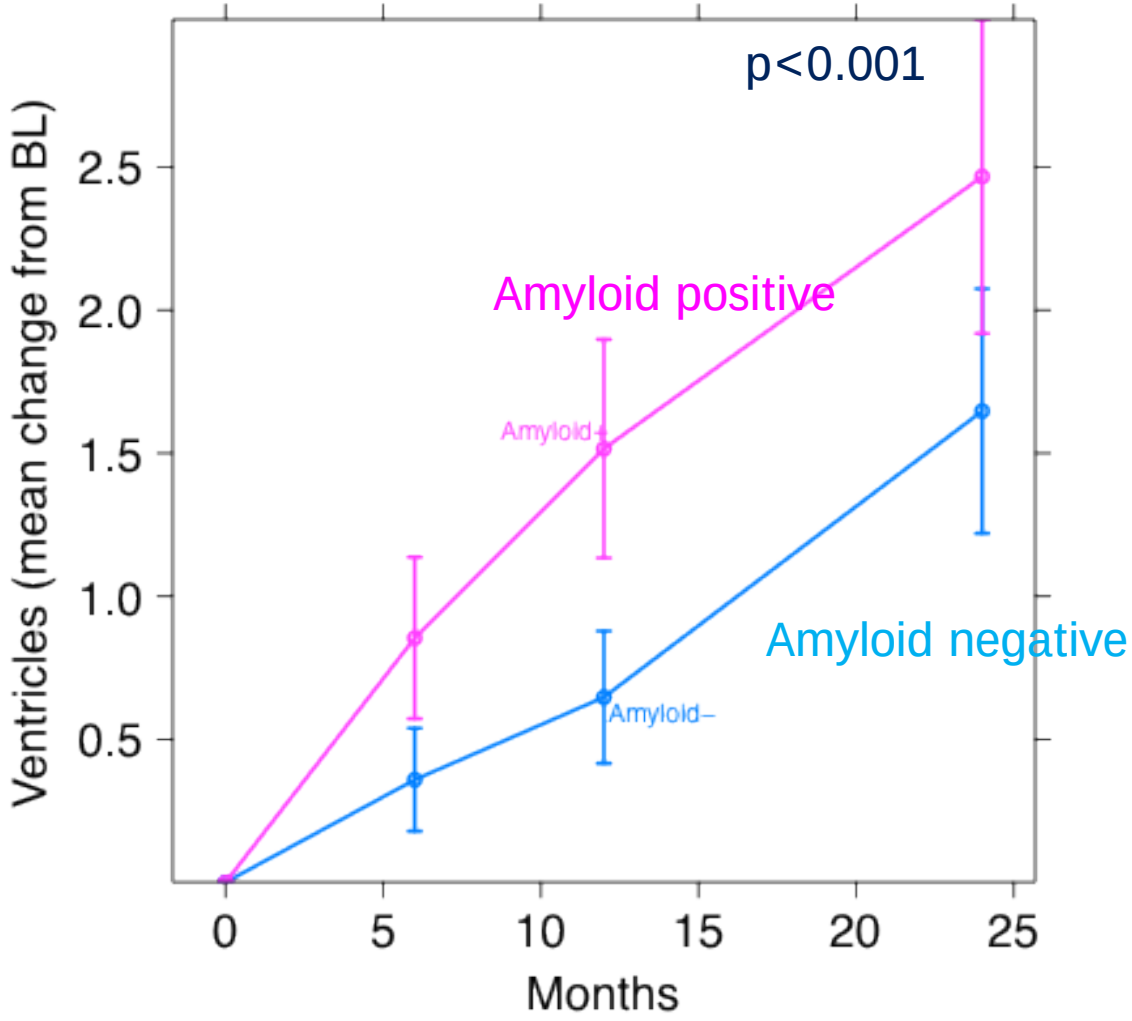
Aisen PS, Petersen RC, Donohue MC, et al. *Alzheimers Dement.* 2010;6:239-246.

AD Diagnosis Marching Leftward

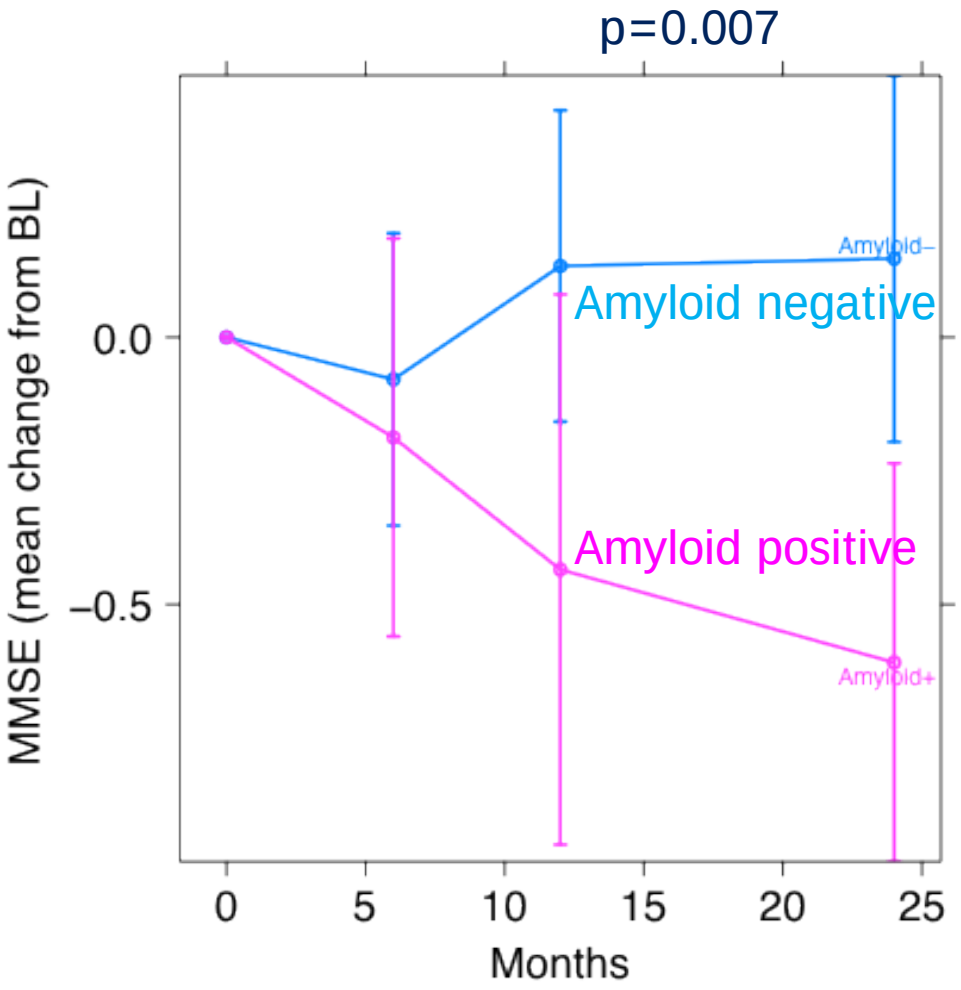


Aisen PS. *Alzheimers Res Ther.* 2009;1:2. doi:10.1186/alzrt2.

Ventricular volume change in normals is linked to amyloid



MMSE change in normals is linked to amyloid



New paradigm

- AD dementia
- Prodromal AD
- Preclinical AD

Amyloid PET imaging is arguably the most important recent advance in AD therapeutic research

- Diagnostic accuracy in AD dementia
- Definition of prodromal AD
- Required for selection of preclinical AD
- Measure of amyloid removal

Clinical value of amyloid PET today

- Negative scan effectively rules out AD
  - Reassurance of worried well
  - Guide any further w/u
- Positive scan effectively assures AD diagnosis in individuals with dementia (one third of APOE4 negatives do not have AD)
- Positive scan will provides prognosis in individuals with MCI

Rates of PET "Amyloid Negativity" at Baseline by APOE carrier status

	Bapineuzumab ^{11}C-PiB	**Solanezumab ^{18}F-AV-45**
APOE ε4 carriers (% Amyloid negative)	6.5	6.6
Non-carriers (% Amyloid negative)	36.1	32.8

What does a positive amyloid-PET scan mean in soemone who is clinically normal?

- Nothing?
- Preclinical AD (will develop AD dementia if individual survives long enough)?

- Suspect the latter, but more longitudinal data needed

Prediction

- When anti-amyloid therapy is approved for preclinical AD, we will screen the population with amyloid PET scans starting in mid-50s

Summary: Amyloid PET imaging

- Enormously important advance
- Pathology no longer required for diagnosis
- Negative scan rules out AD
- Positive scan plus dementia syndrome confirms AD
- Prognostic in MCI
- Essential for therapeutic research; early AD trials

- In most cases of AD dementia, diagnosis requires only skillful interviews and brief mental status examination