Incorporating Biomarkers of Amyloid and Neurogeneration in Clinical Evaluation of Mild Cognitive Impairment

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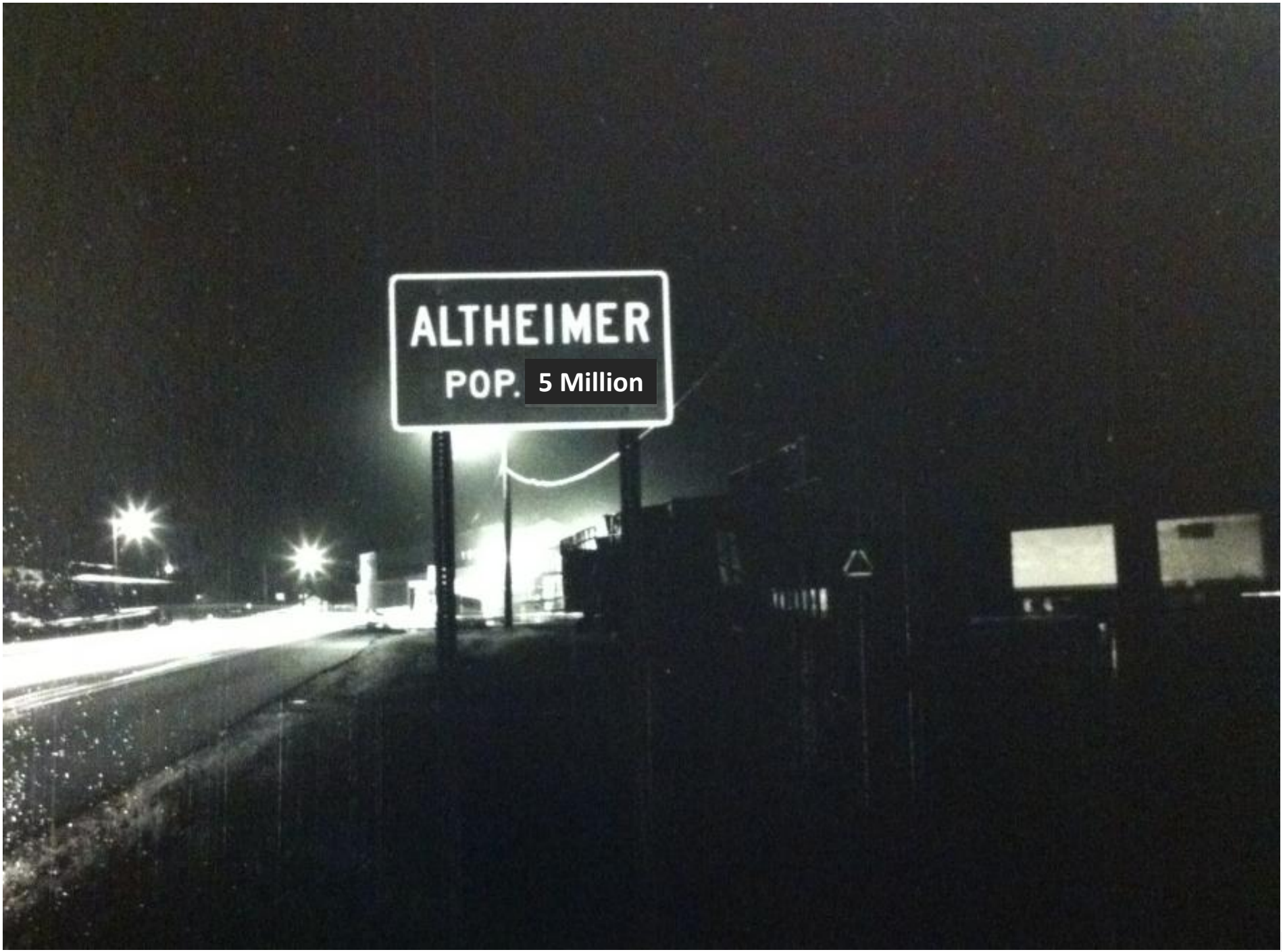
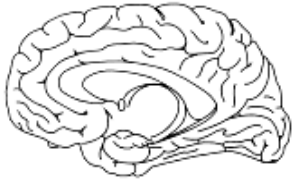
Disclosures: Nothing to disclose

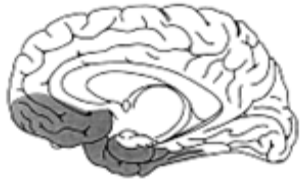

ALTHEIMER
POP. 5 Million

Clinical and Pathological Course of AD

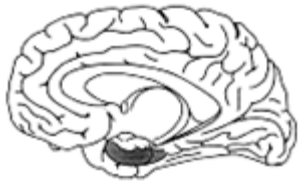
Clinical State	**Normal**	**Pre-Clinical AD**	**MCI**	**AD**
Cognitive State	**No Symptoms**	**No Symptoms?**	**Mild Symptoms**	**Mild-Severe Symptoms**
Pathologic State	**No Disease**	**Early Changes**	**Mild Mod Changes**	**Mod-Severe Changes**

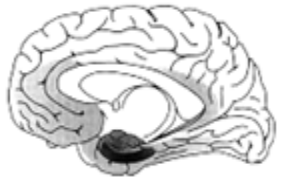
Plaques ⇨

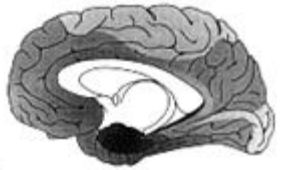




Tangles ⇨



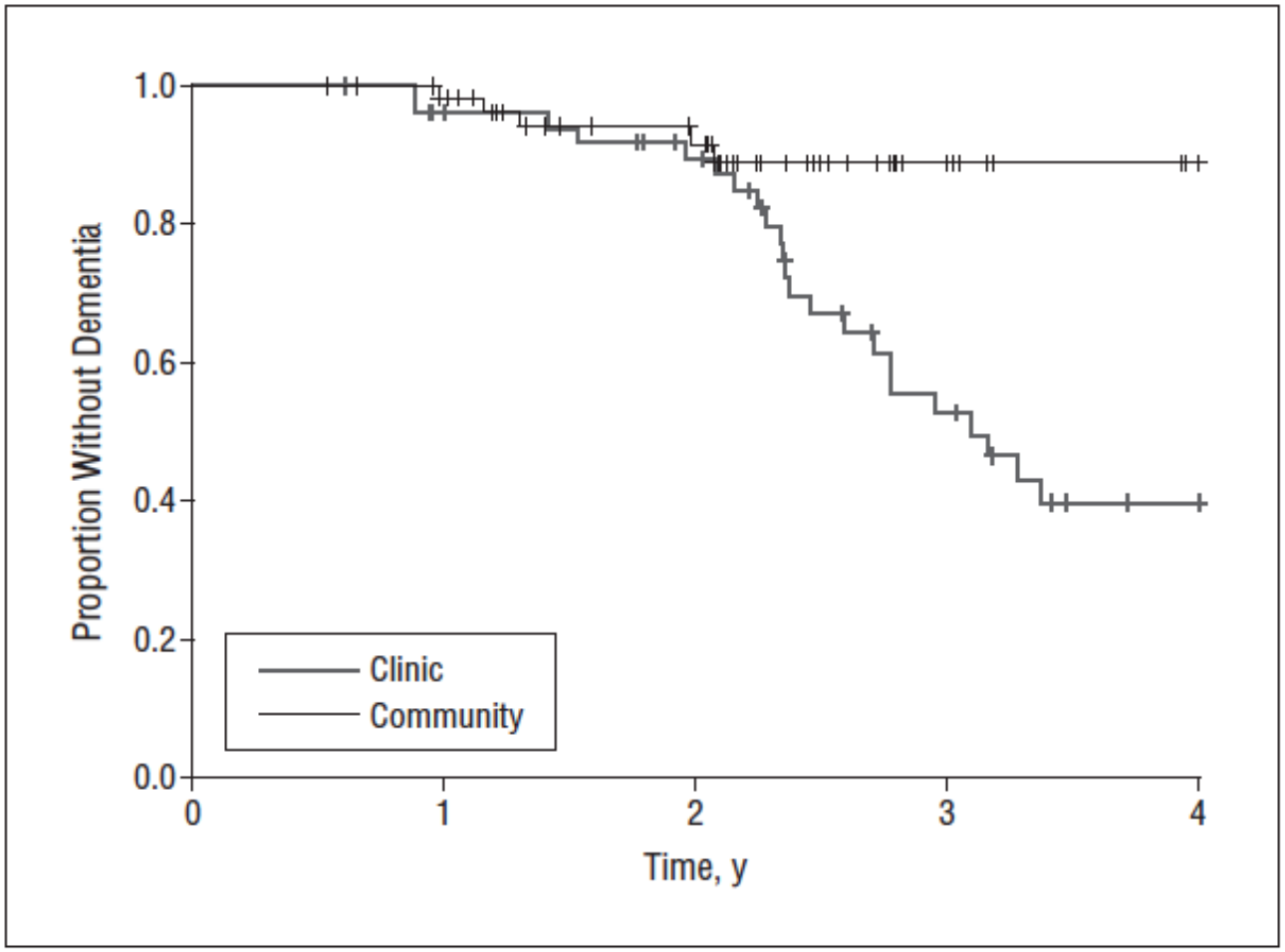




“Petersen Criteria” for MCI

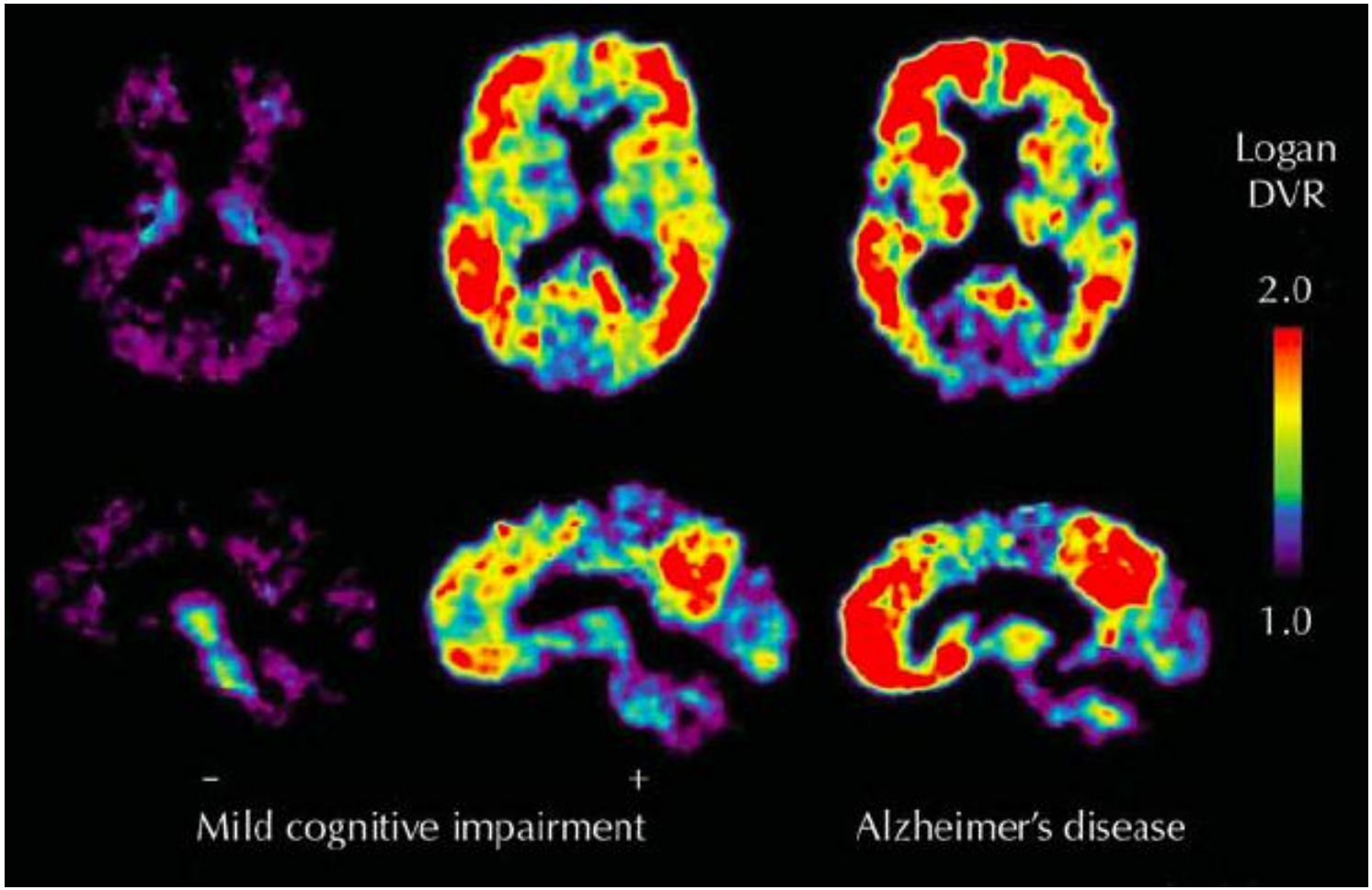
- Cognitive complaint (preferably corroborated by informant)
- Objective impairment for age and education
- Largely intact general cognitive function
- Essentially preserved activities of daily living
- Not demented

MCI Enriched in Patients with Prodromal AD



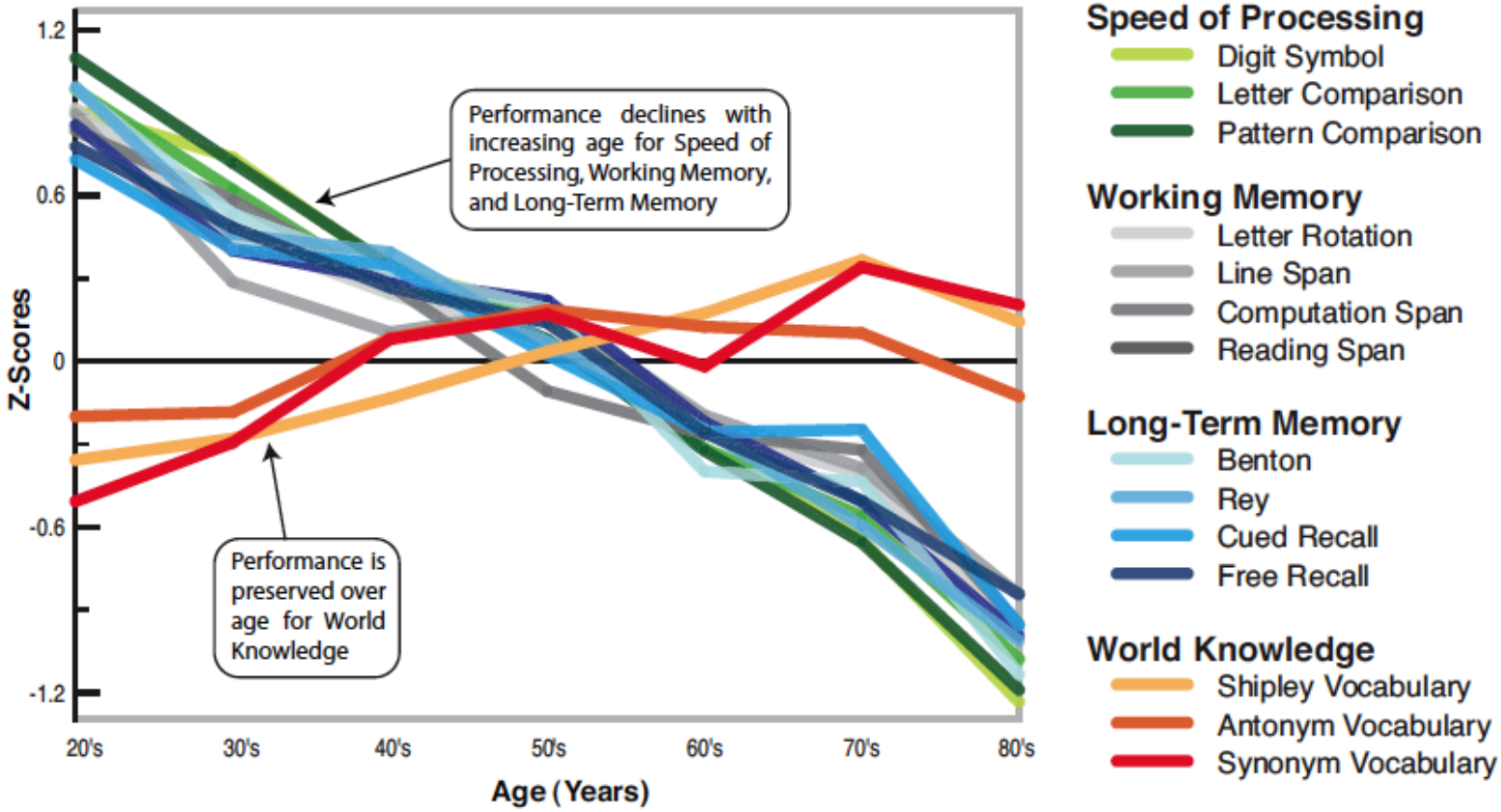
Tomaszewski Farias S et al. *Arch Neurol*. 2011;66:1151-1157.

Amyloid Imaging in MCI – 50-70% “Positive”



Wolk DA, Klunk WE. *Curr Neurol Neurosci Rep*. 2009;9:345-352.

Age-Associated Cognitive Impairment



Park DC, Reuter-Lorenz P. *Annu Rev Psychol*. 2009;60:173-196.

Mild Cognitive Impairment

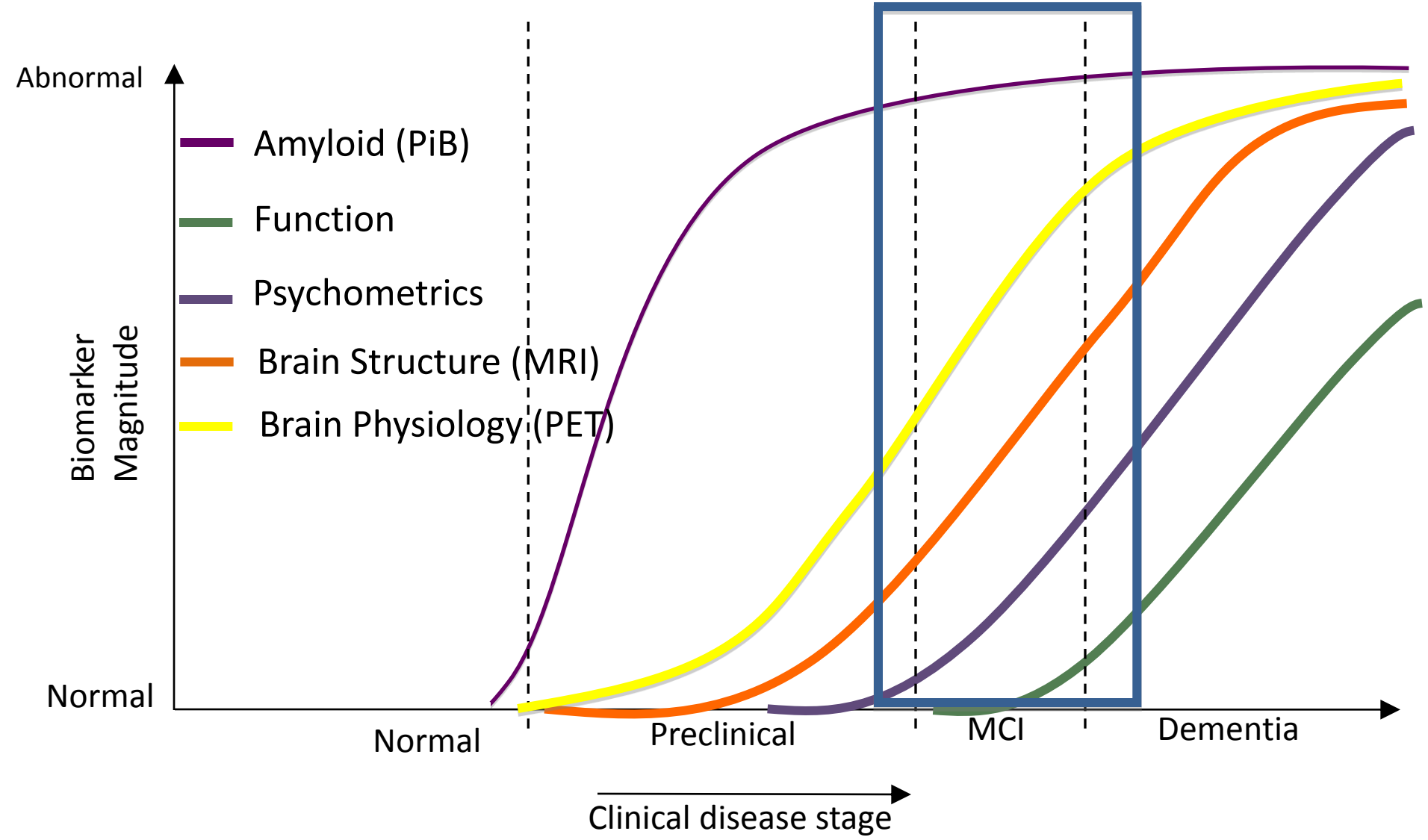
- Heterogeneous Population
  - AD
  - Other neurodegenerative disorders
  - Age-Associated memory loss
    - At border of diagnosis of MCI
  - CVD
  - Hippocampal sclerosis
  - Depression
  - Medications

Peterson RC. *N Engl J Med*. 2011;364:2227-2234.

Additional Tests May Enhance Accuracy of Diagnosis – "Biomarkers of AD"

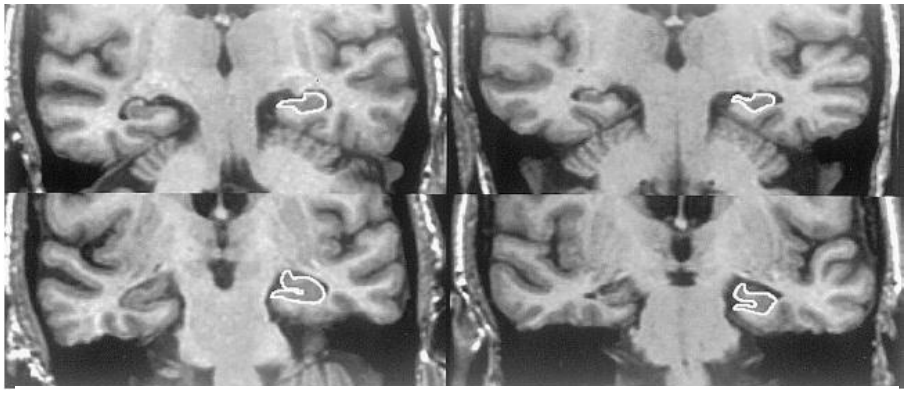
- Markers of Brain Degeneration
  - Look for evidence of brain changes in pattern consistent with AD
  - Structural MRI (atrophy), Glucose PET scans, CSF tau/p-tau
- Markers of Brain Pathology
  - Look for molecular evidence of AD
  - Cerebrospinal Fluid (CSF), "Amyloid Imaging"

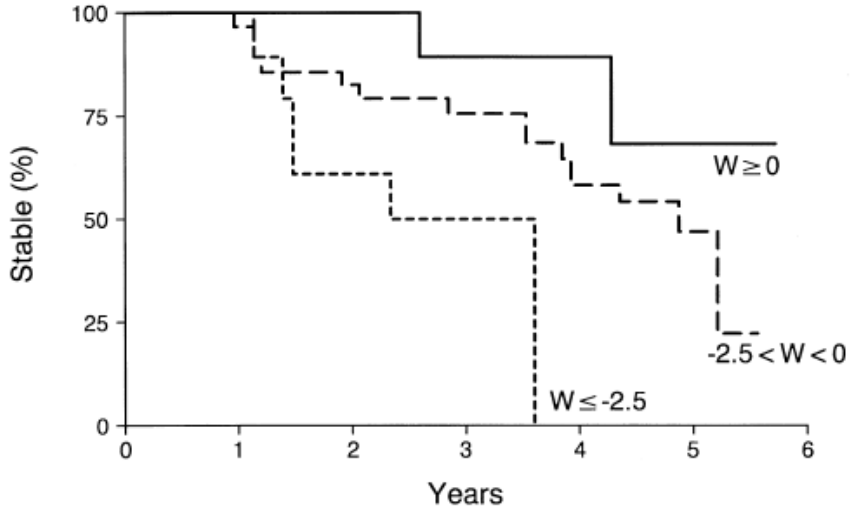
Dubois B et al. *Lancet*. 2007;6:734-746.

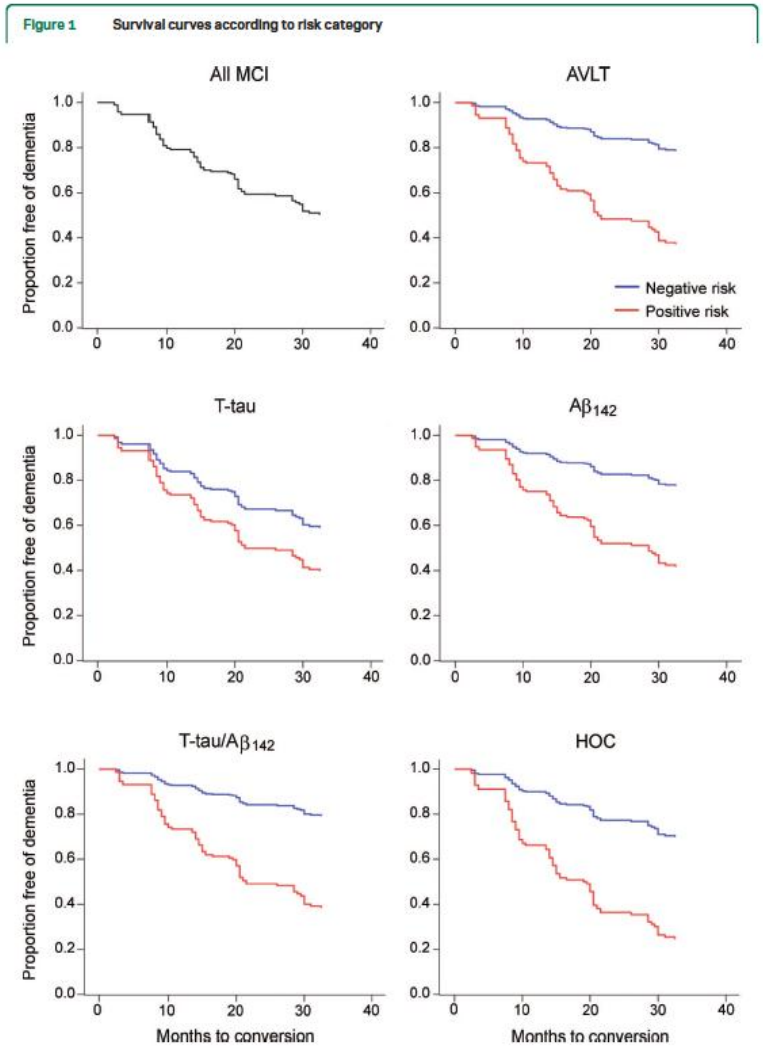


Modified from Jack CR Jr et al. *Lancet Neurol*. 2010;9:119.

Biomarkers Enhance Prediction of Conversion



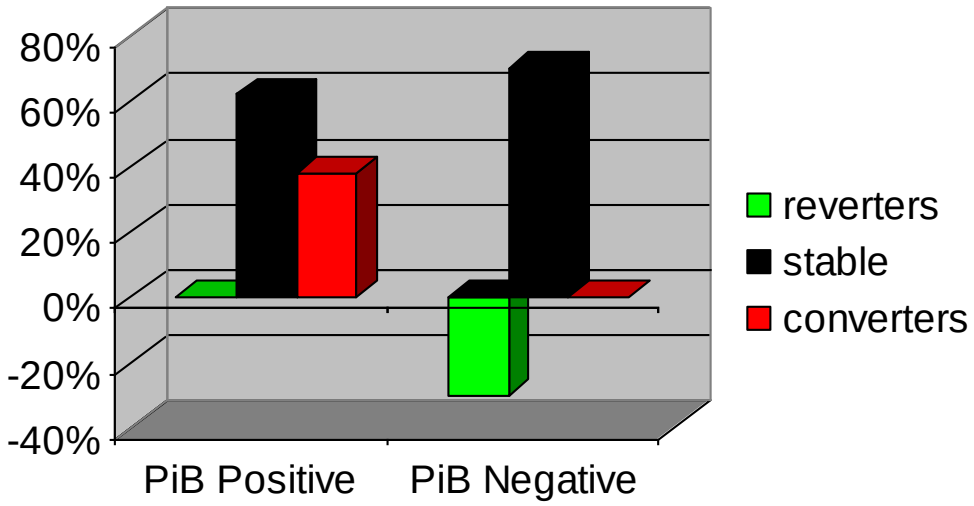




Jack CR Jr et al. *Neurology*. 1999;52:1397-1403.
Heister D et al. *Neurology*. 2011;77:1619-1628.

Amyloid Imaging and Conversion to AD in MCI

- 23/26 patients have had follow-up ADRC evaluations and consensus discussion
  - Overall mean f/u: 21.2 months (6-57 months)
  - 13 PiB positive (Mean: 21.9 months)
  - 10 PiB negative (Mean: 22.3 months)



Wolk DA et al. *Ann Neurol*. 2009;65:557-568.

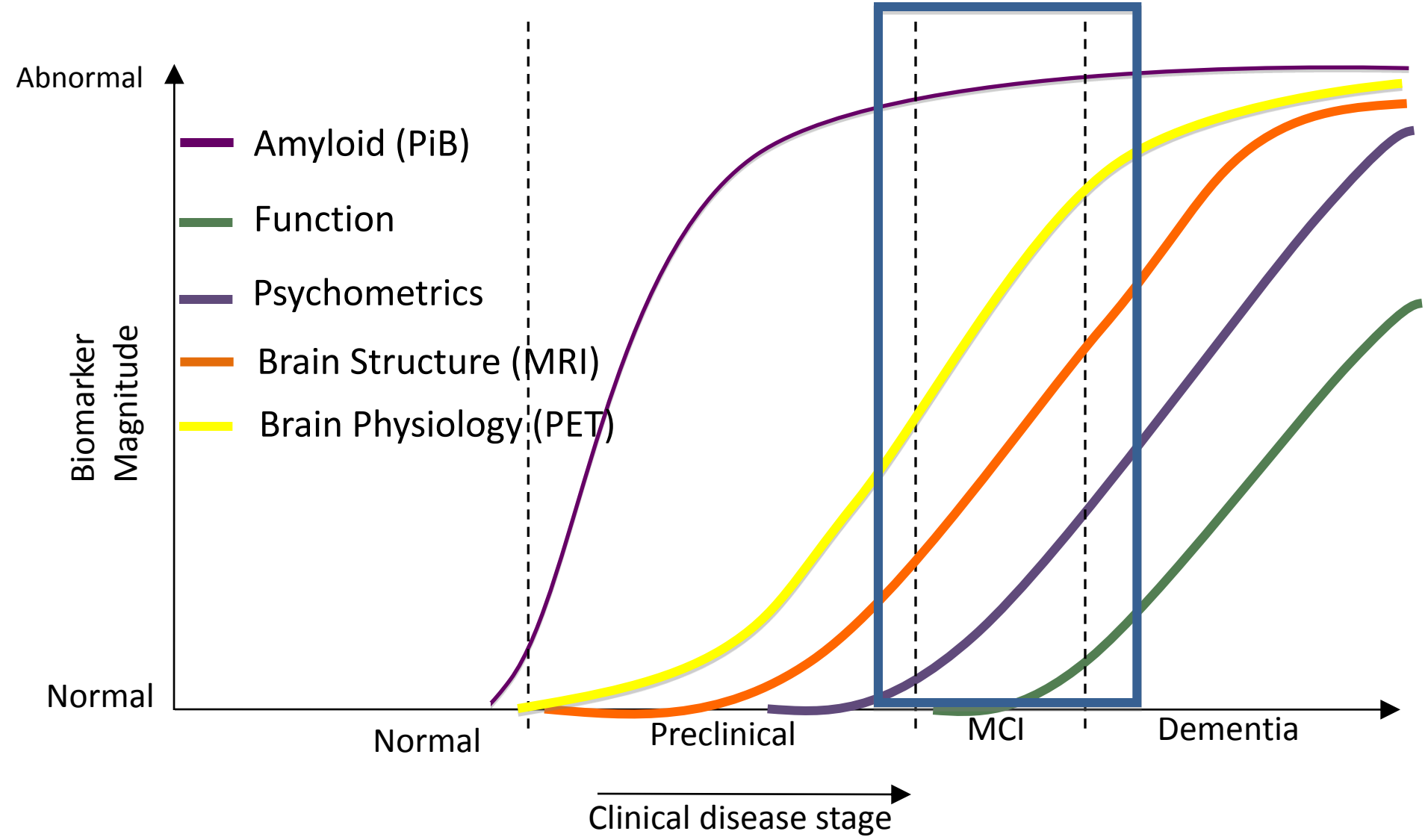
NIA-AA MCI Criteria

Diagnostic Category	Biomarker Driven Probability of AD Etiology	Presence of Cerebral Amyloidosis (PET, CSF)	Evidence of Neuronal Injury (tau, FDG, sMRI)
MCI-core clinical criteria	Uninformative	Conflicting/indeterminite/untested	Conflicting/indeterminite/untested
MCI due to AD – Intermediate likelihood	Intermediate	Positive	Untested
		Untested	Positive
MCI due to AD – High likelihood	Highest	Positive	Positive
MCI – unlikely due to AD	Lowest	Negative	Negative

Albert et al., *Alzheimer's & Dementia*, 2011

NIA-AA MCI Criteria

- Do these biomarkers provide differential information about the timing of progression?
- Conflicting results considered “uninformative”
  - What is the meaning of discordance between amyloid and neurodegenerative measures
    - Likelihood of AD etiology?
    - Likelihood of progression?
  - Does it matter which measure (amyloid vs. neurodegenerative) is positive or negative?



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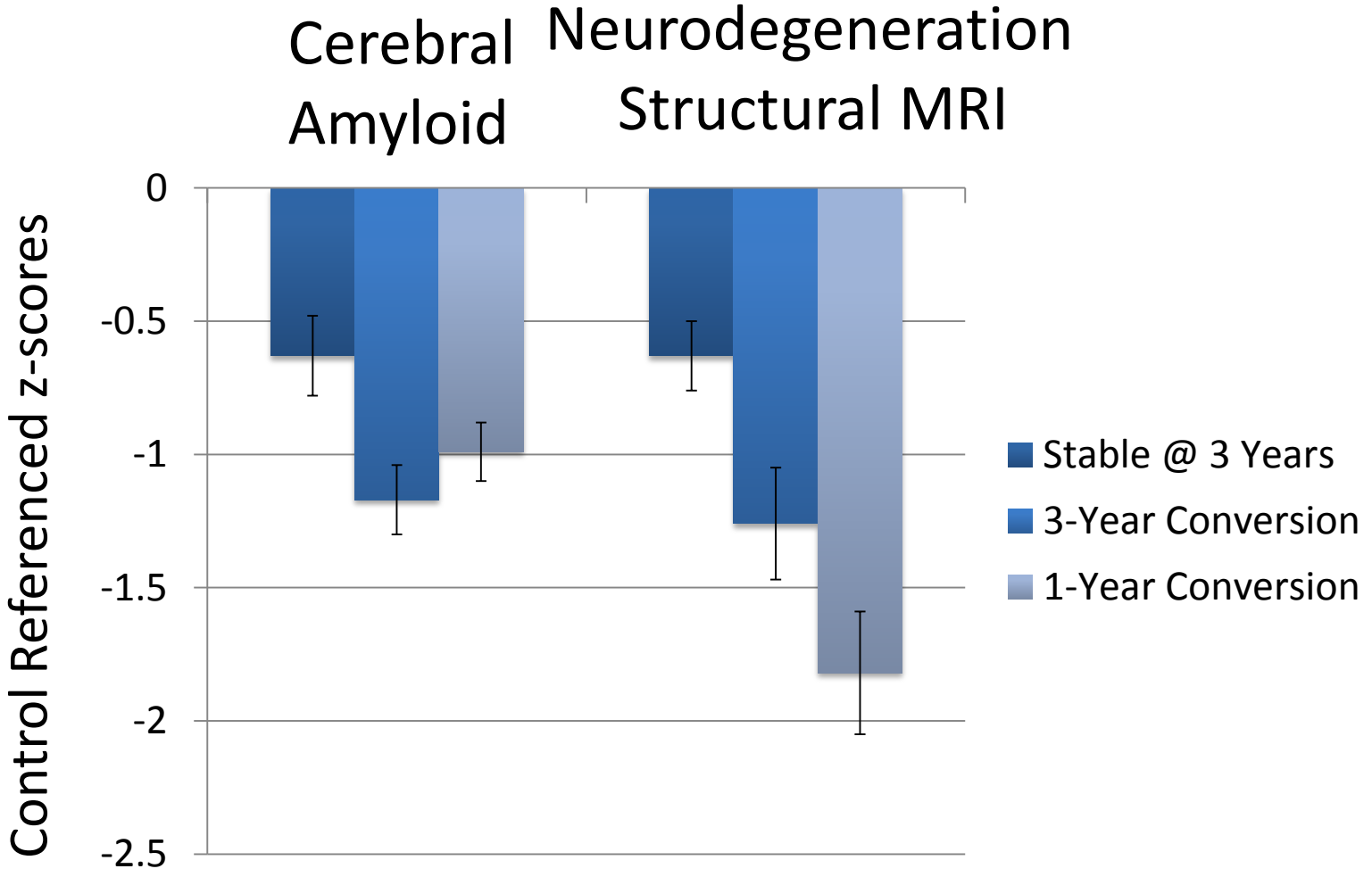
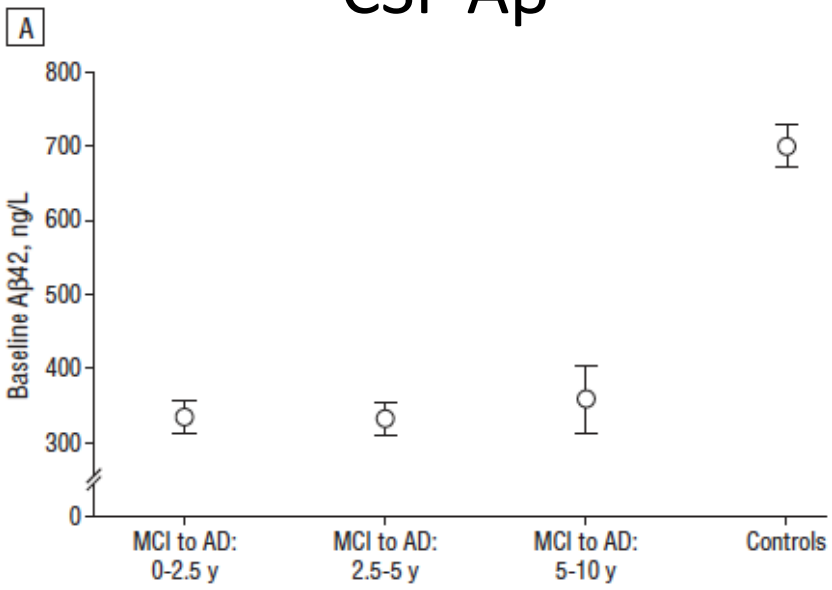
Relationship of Amyloid and Neurodegeneration to Time of Progression



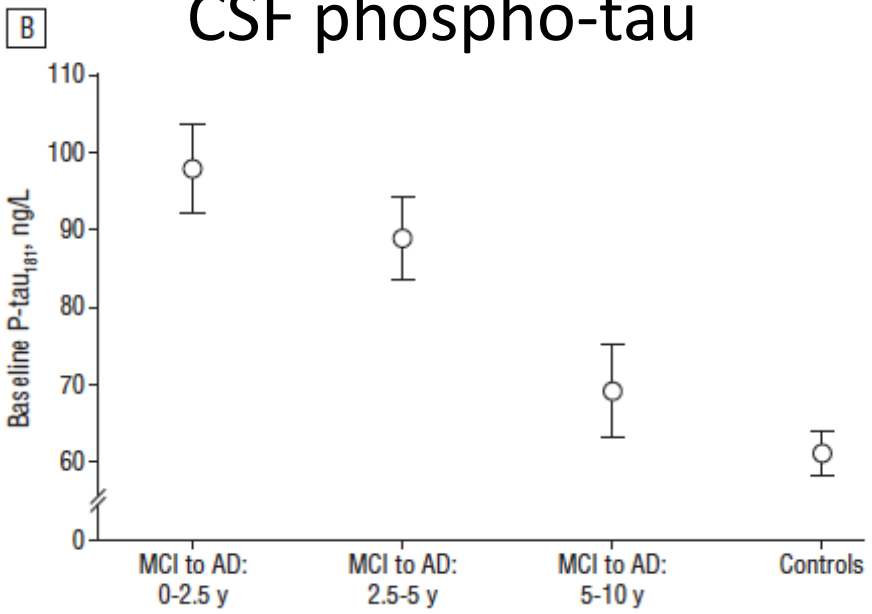
Dickerson & Wolk, *Frontiers in Aging Neuroscience*, 2013

P-Tau Tracks Timing of Conversion

Cerebral Amyloid: CSF Aβ



Neurodegeneration: CSF phospho-tau

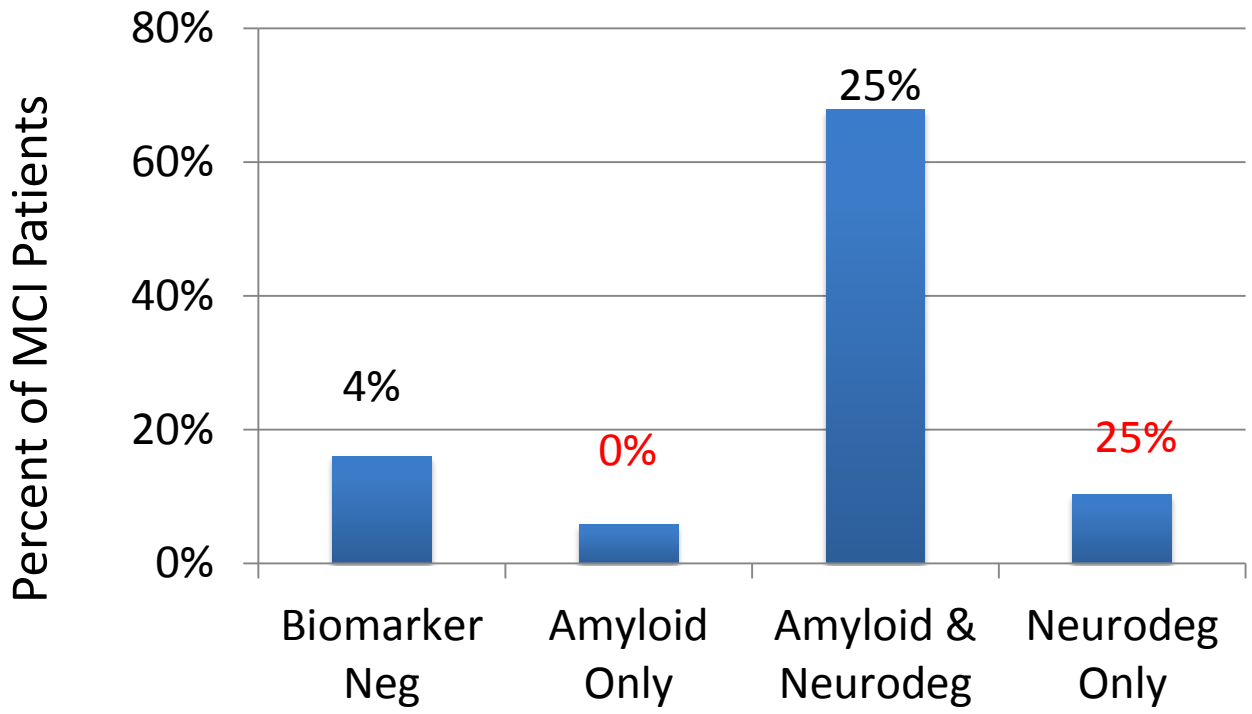


Buchhave et al., *Archives Gen Psychiatry*, 2011

Categorization Based on Biomarkers

- Concordant Findings
  - Amyloid negative, neurodegeneration negative
    - Low likelihood AD
  - Amyloid positive, neurodegeneration positive
    - High likelihood AD
- Discordant Findings
  - Amyloid positive/neurodegeneration negative or amyloid negative/neurodegeneration positive
    - Uninformative
- Most importantly, what do these different groupings mean for an individual's likelihood of progression?

MCI Biomarker Groups



What is Underlying Cause and Outcome of Each Group

- Biomarker negative
  - Unlikely AD, Low rate of conversion
- Amyloid + Neurodegeneration
  - High likelihood of AD and high conversion rate
- Amyloid only
  - Earlier in disease course versus symptoms not due to amyloid pathology
  - Low near-term conversion to dementia
- Neurodegeneration Only
  - Non-AD neurodegeneration versus modification of typical biomarker cascade (neurodegeneration precedes detectable amyloid)
  - Significant proportion develop dementia

Conclusions

- Biomarkers enhance certainty of diagnosis
- Neurodegenerative markers may provide more specific information about the timing of progression
  - Allows for earlier treatment and appropriate planning
- Concordant biomarkers provide most certainty with regard to outcomes
- Other combinations less clear and represent an important area for further research
  - In particular, neurodegeneration only group displays high rate of conversion and relatively specific AD pattern despite absence of biomarker evidence for cerebral amyloidosis

Thank You!!

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