Alzheimer's Disease Biomarkers in the Community

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MCI Symposium

Miami

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Disclosures

- Roche, Inc.
- Merck, Inc.
- Genentech, Inc.
- Biogen, Inc.
- Eli Lilly and Co.
- Funding
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  - U01 AG006786
  - P50 AG016574
  - U01 AG011378
  - R01 AG011378
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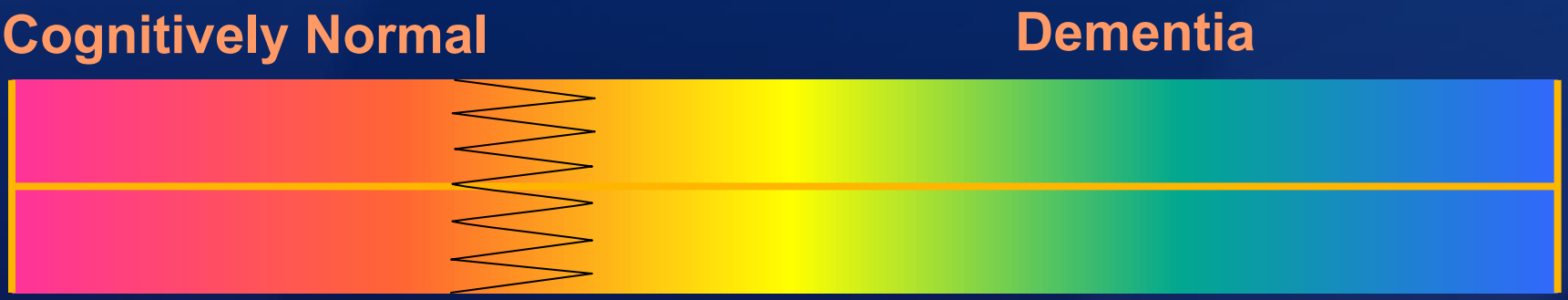
  - Mayo Foundation for Education and Research

Old Conception of Alzheimer's Disease



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Cognitive Continuum

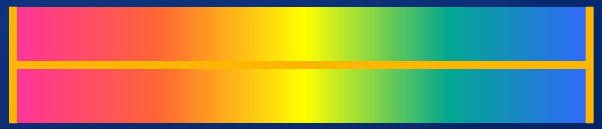
Normal

MCI

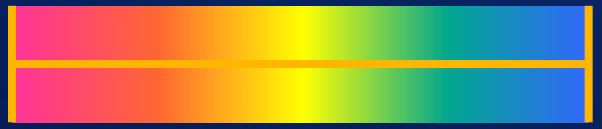
Dementia

Alzheimer's Disease Spectrum

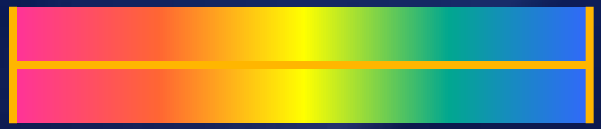
Preclinical AD



MCI Due to AD



Dementia Due to AD



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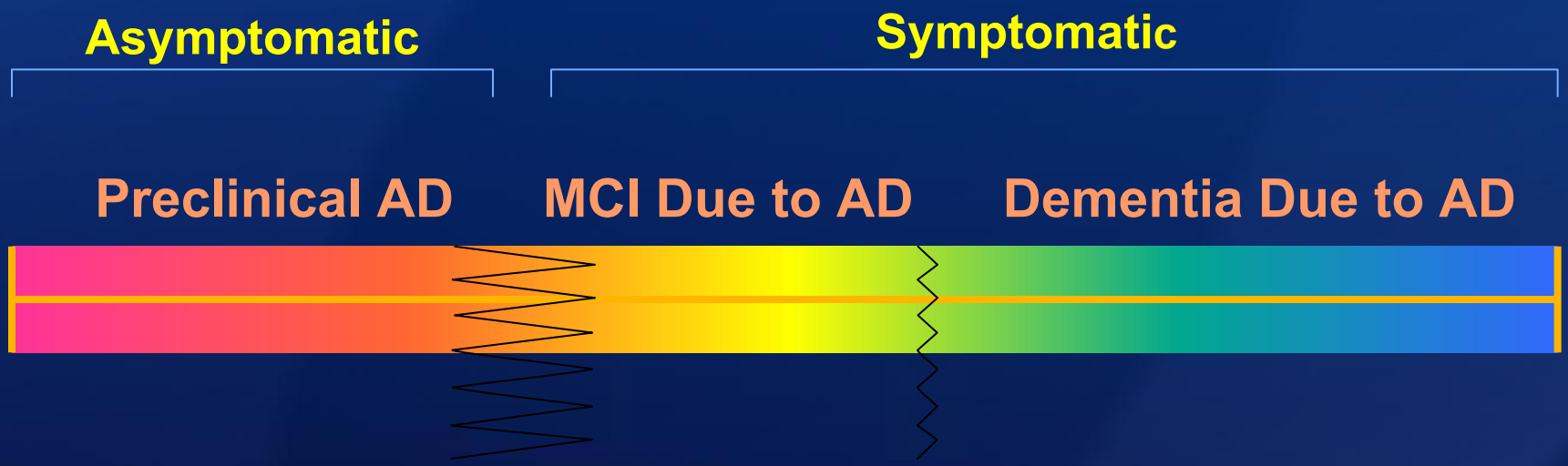
Alzheimer's Disease Spectrum



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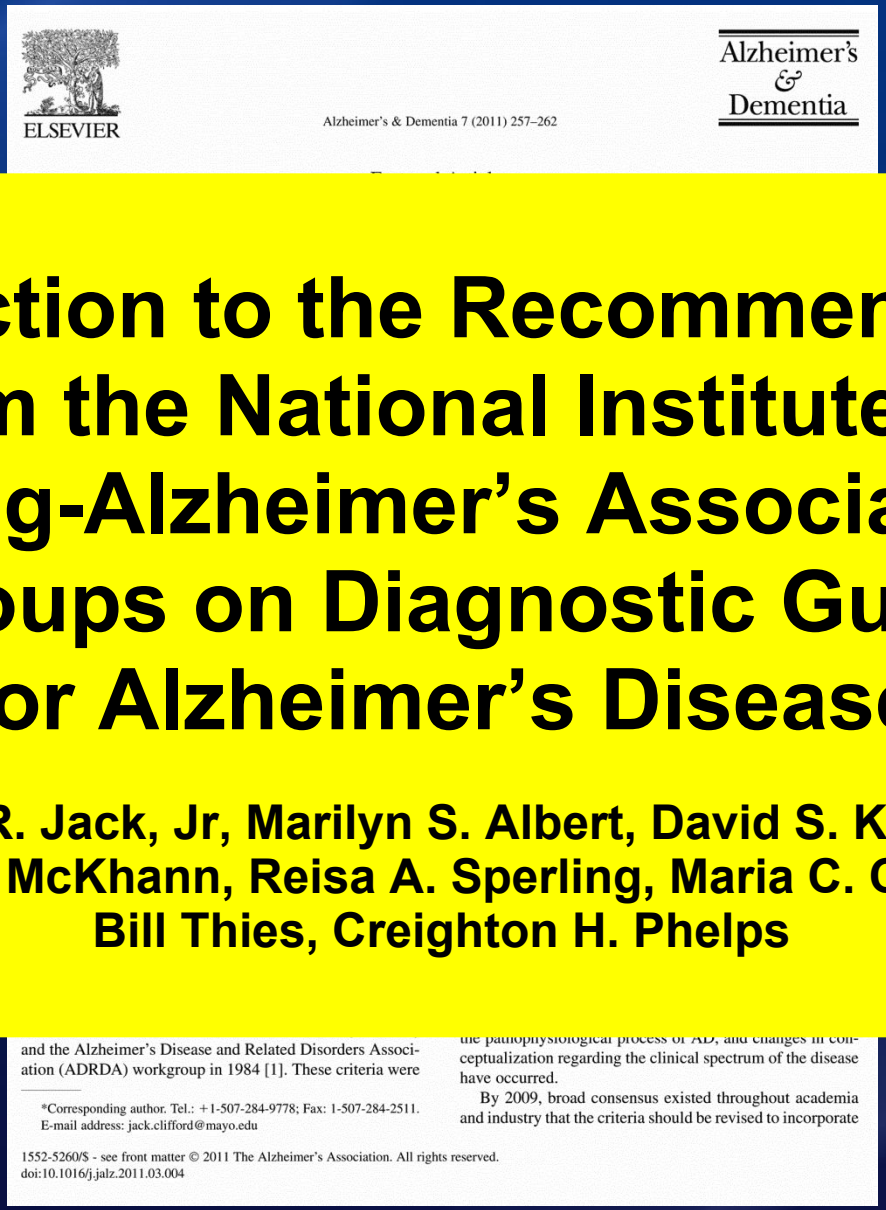
ELSEVIER

Alzheimer's & Dementia 7 (2011) 257–262

Alzheimer's & Dementia

Introduction to the Recommendations from the National Institute on Aging-Alzheimer's Association Workgroups on Diagnostic Guidelines for Alzheimer's Disease

Clifford R. Jack, Jr, Marilyn S. Albert, David S. Knopman, Guy M. McKhann, Reisa A. Sperling, Maria C. Carrillo, Bill Thies, Creighton H. Phelps

and the Alzheimer's Disease and Related Disorders Association (ADRDA) workgroup in 1984 [1]. These criteria were

the pathophysiological process of AD, and changes in conceptualization regarding the clinical spectrum of the disease have occurred.

By 2009, broad consensus existed throughout academia and industry that the criteria should be revised to incorporate

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doi:10.1016/j.jalz.2011.03.004

Alz and Dementia, 2011

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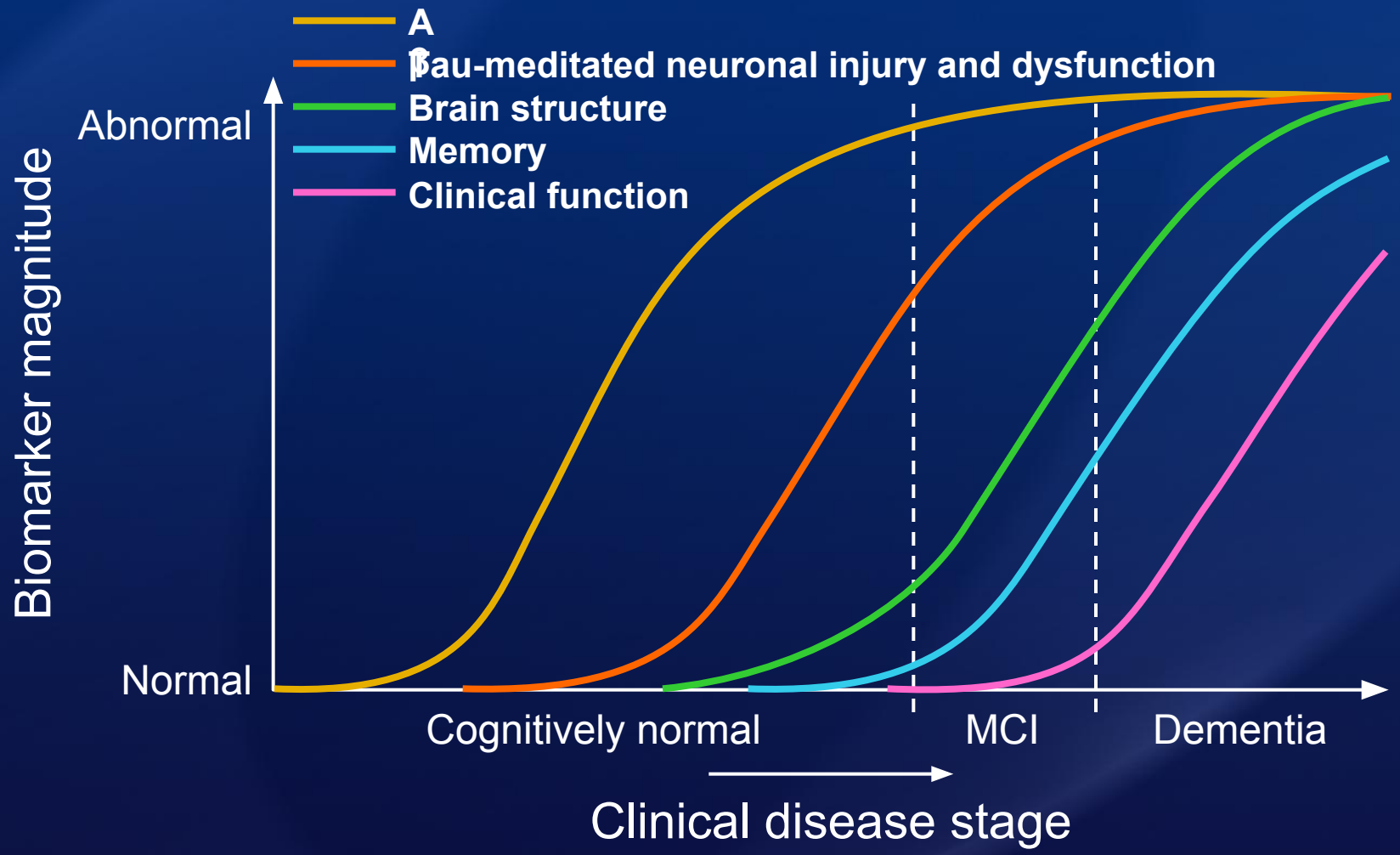
Hypothetical Model of Dynamic Biomarkers of the Alzheimer's Pathological Cascade



Jack et al: Lancet Neurol 2010

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Neuroimaging in AD

Neuroimaging in AD

- Structural MRI
- Functional imaging
  - FDG PET
- Molecular imaging
  - Amyloid PET imaging
  - Tau PET imaging

Structural Imaging in AD

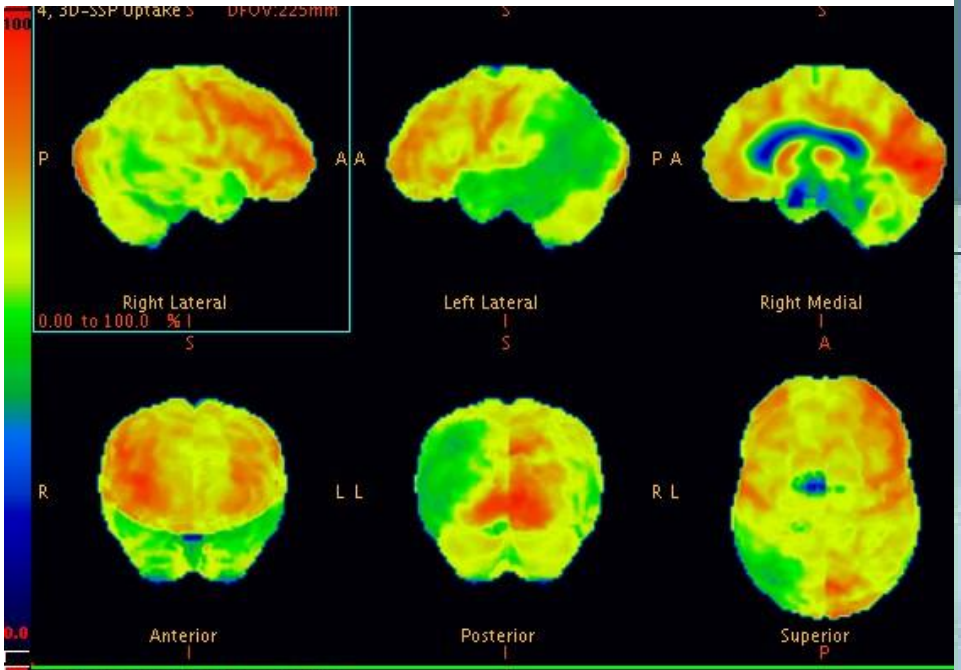
Structural MRI: Atrophy and AD Stage

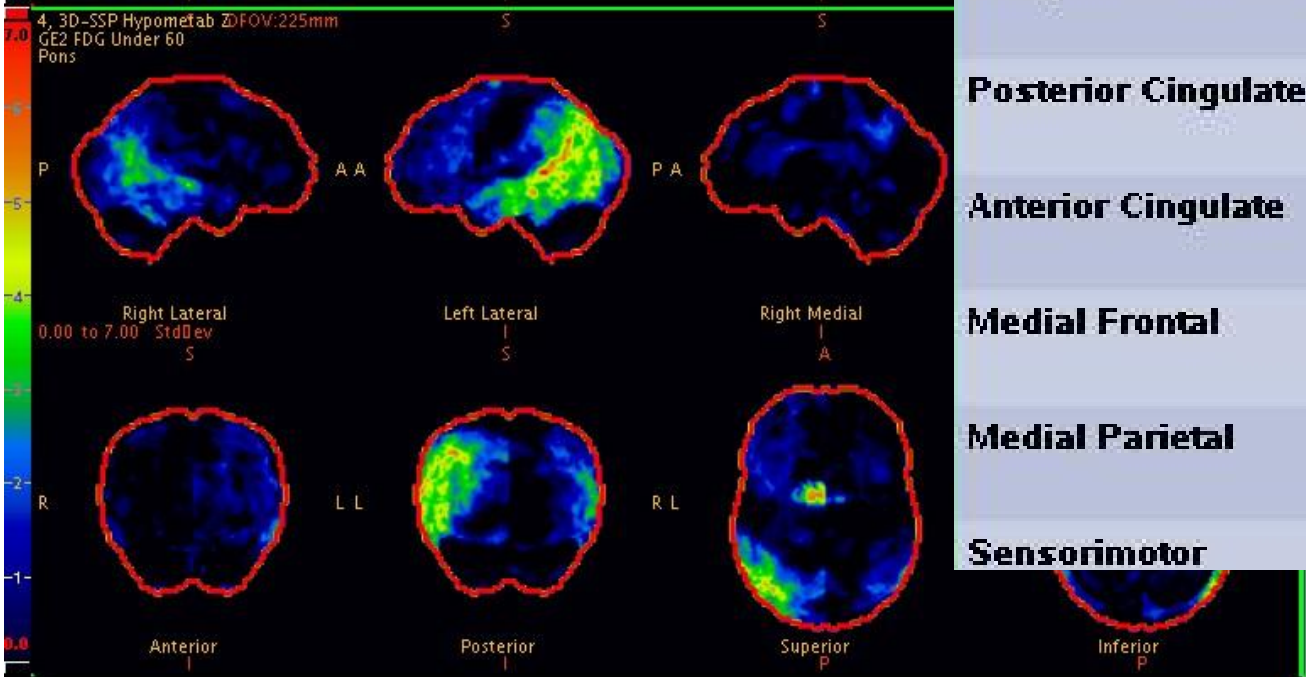
Control, 70, F

MCI, 72, F

AD, 74, F

Functional Imaging in AD





(Z-Score)

Normals File: GE2 FDG Under 60

Normalized By: Pons

Cortical Regions	R/L	Mean
Parietal Association	R	0.91
	L	2.84
Temporal Association	R	1.41
	L	2.72
Frontal Association	R	-0.19
	L	0.75
Occipital Association	R	0.72
	L	2.55
Posterior Cingulate	R	0.09
	L	0.38
Anterior Cingulate	R	0.05
	L	0.10
Medial Frontal	R	-0.17
	L	0.57
Medial Parietal	R	0.17
	L	1.35
Sensorimotor	R	-0.45

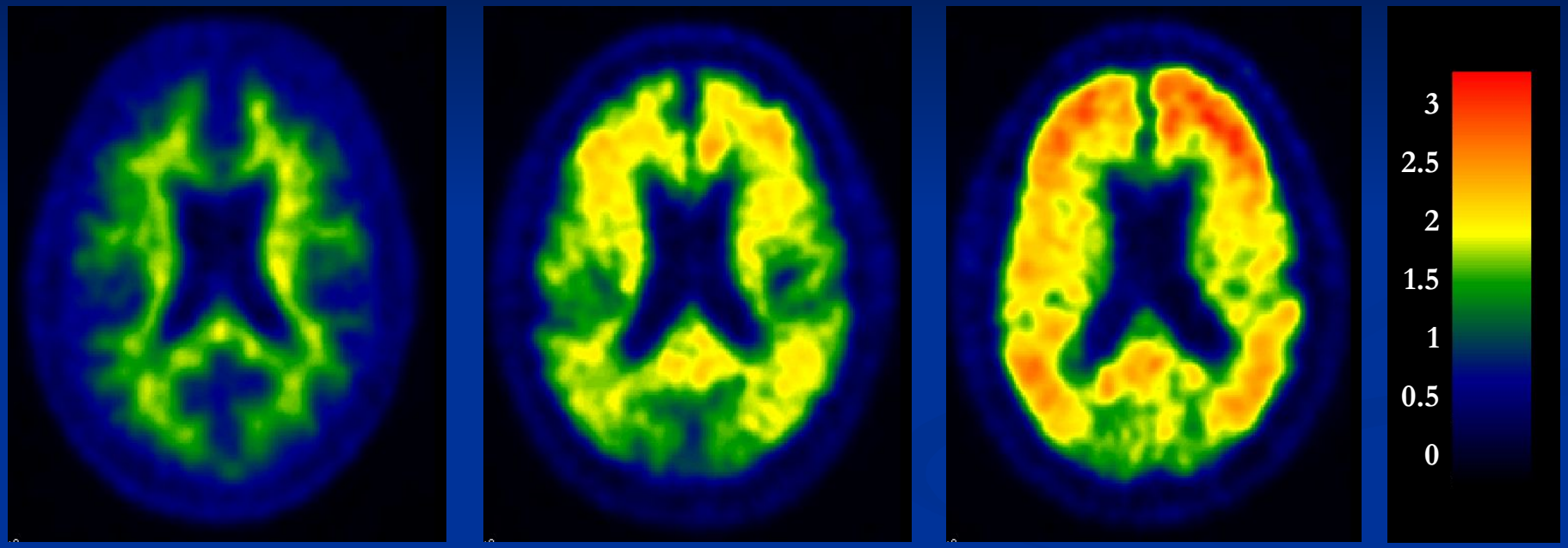
Molecular Neuroimaging

PIB Idealized

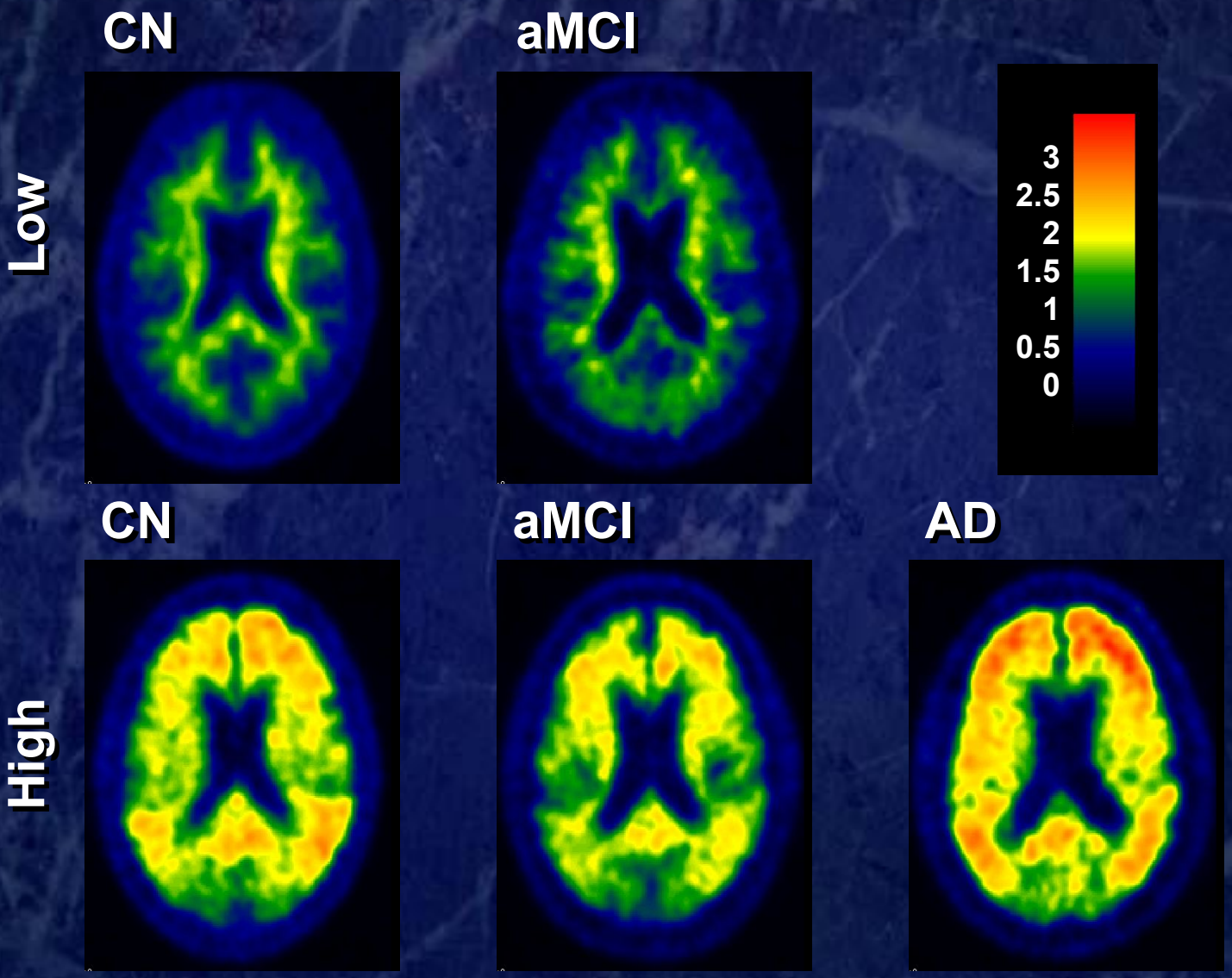
CN

aMCI

AD



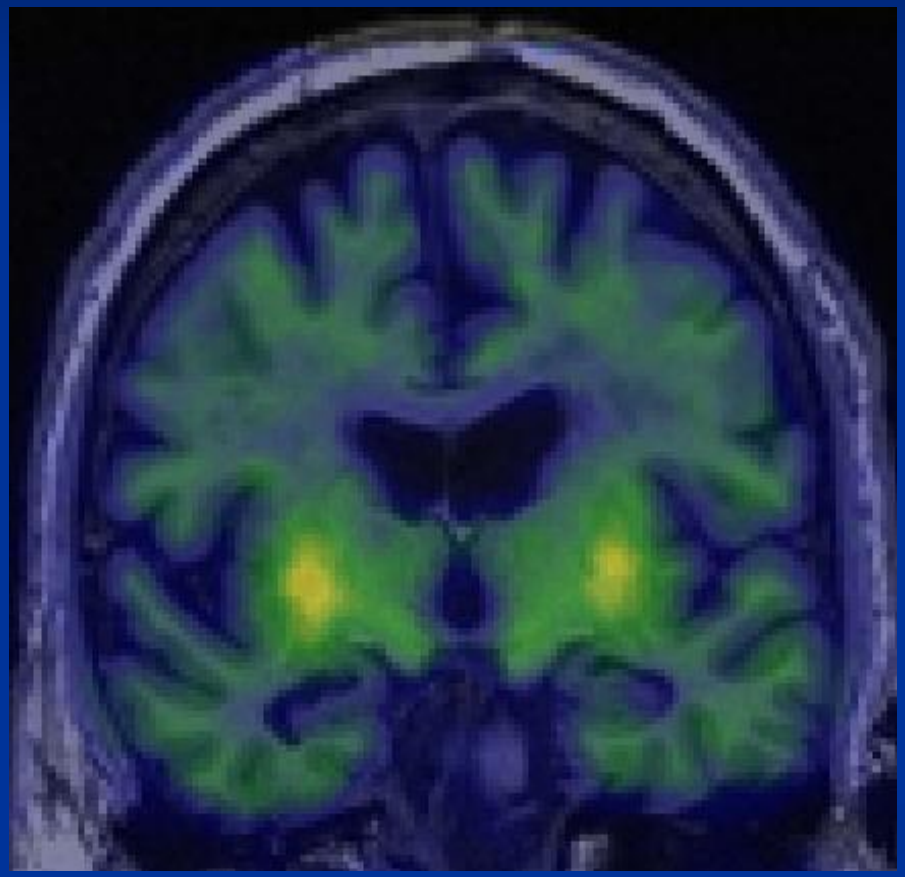
PIB Examples – Full Spectrum



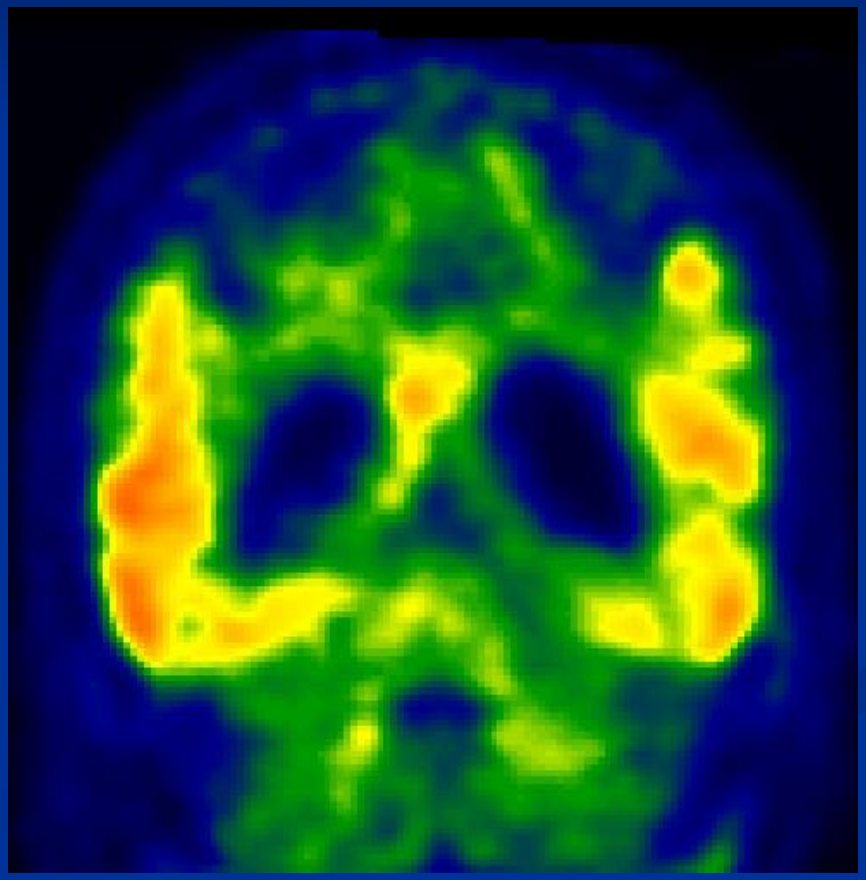
Tau PET

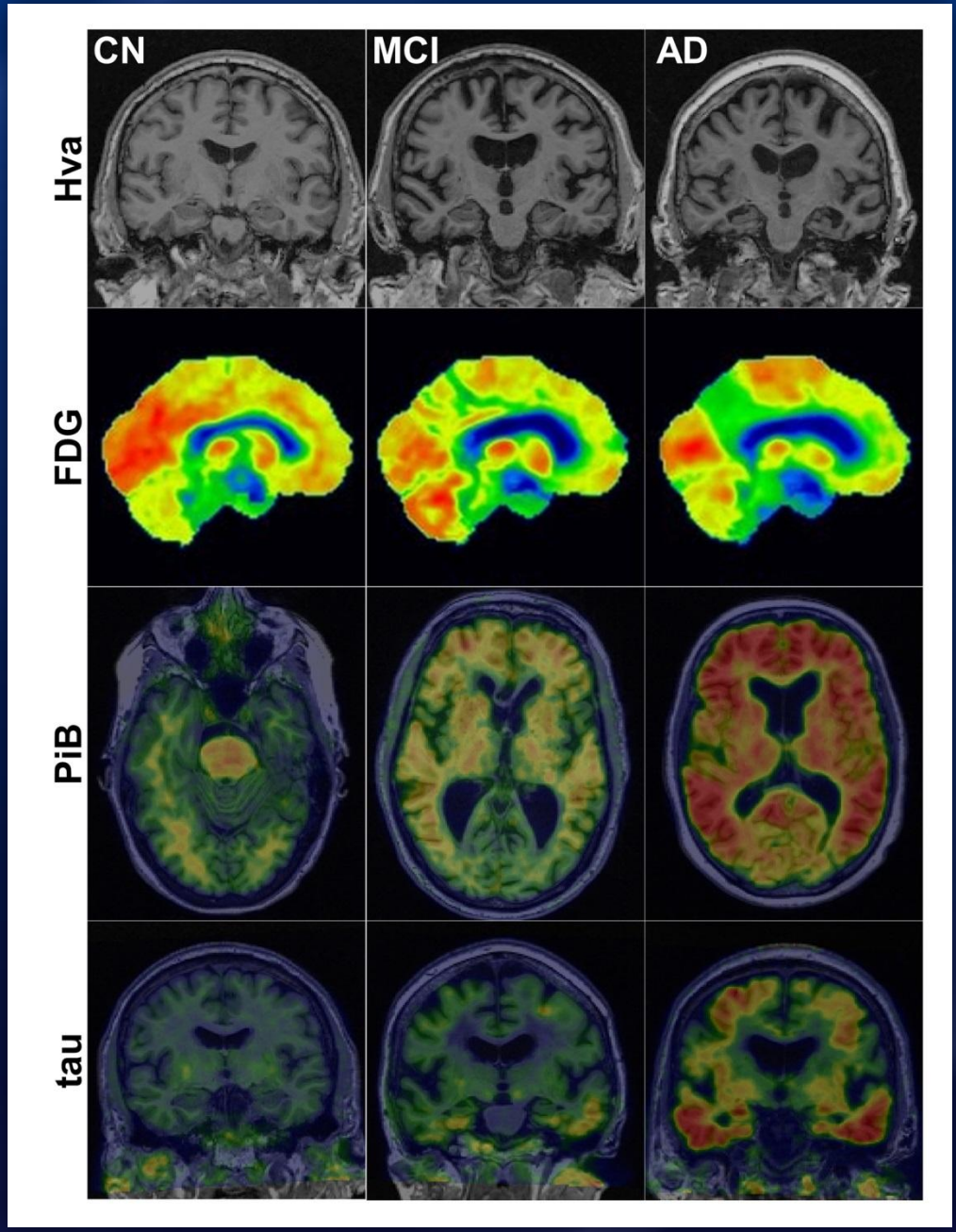
Tau PET

Clinically normal
84yo



AD dementia 71yo





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Alzheimer's Disease Spectrum

Preclinical AD

MCI Due to AD

Dementia Due to AD

Dementia Due to AD

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (tau, FDG, sMRI)
Probable AD dementia	Uninformative/ available	Conflicting/ indeterminant or unavailable	
Probable AD with evidence of path AD	Intermediate Highest	? Positive	Positive Positive
Possible AD dementia atypical with path	High consider secondary	Positive	Positive
Dementia unlikely AD	Lowest	Negative	Negative

McKhann et al: 2011

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MCI Due to AD

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (tau, FDG, sMRI)
MCI	Uninformative	Conflicting/ indeterminant or unavailable	
MCI due to AD – intermediate likelihood	Intermediate 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: 2011

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Preclinical AD

Diagnostic category	Aβ (PET or CSF)	Neuronal injury	Clinical
Stage 1	Positive	Negative	Negative
Stage 2	Positive	Positive	Negative
Stage 3	Positive	Positive	Positive
Stage 0	Negative	Negative	Negative

Sperling et al: 2011

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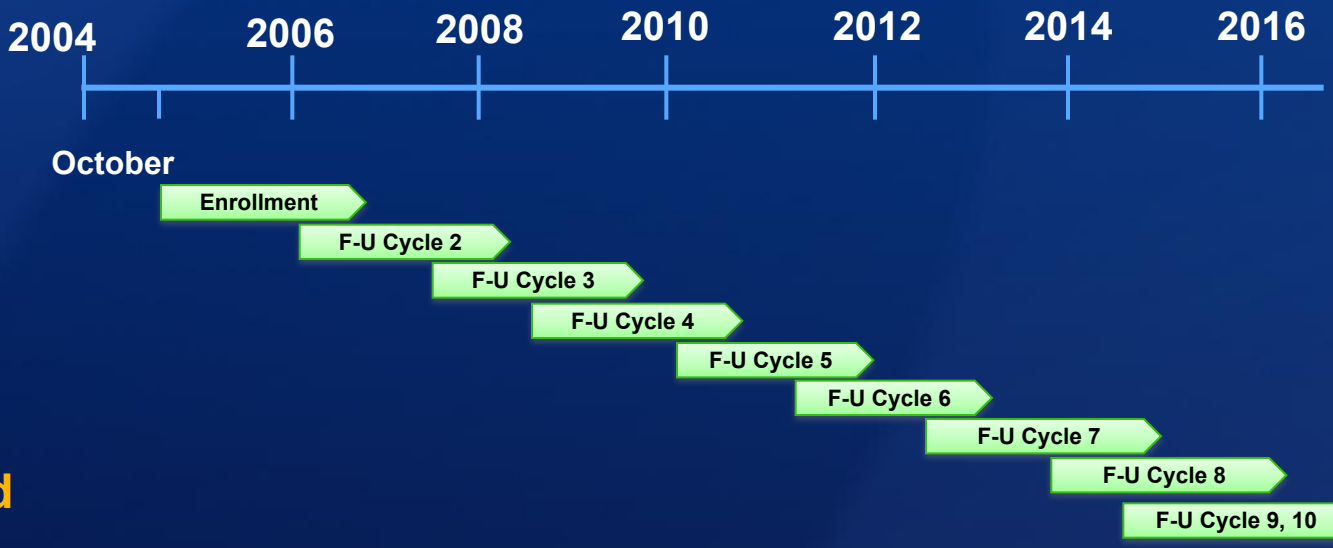
Mayo Clinic Study of Aging (U01 AG006786)

Mayo Clinic Study of Aging

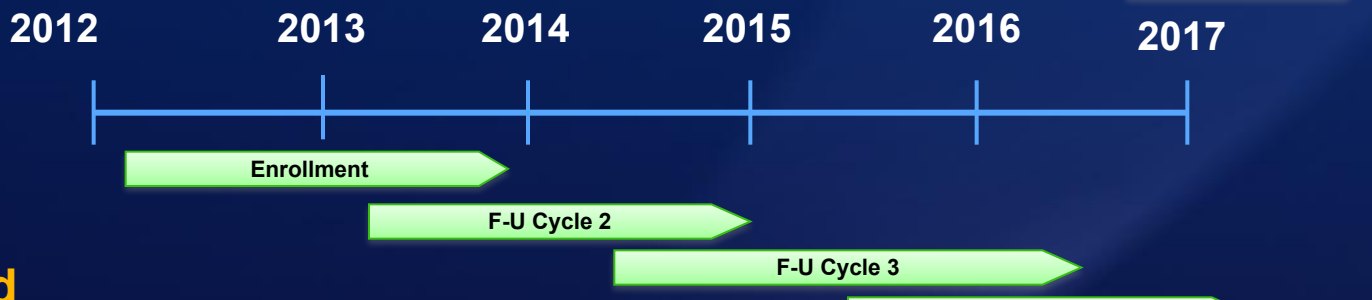
Population-based study of 5000+ (2800 active) nondemented persons age 30-89 years in Olmsted County, MN

MCSA Cycles of Recruitment and Follow-Up

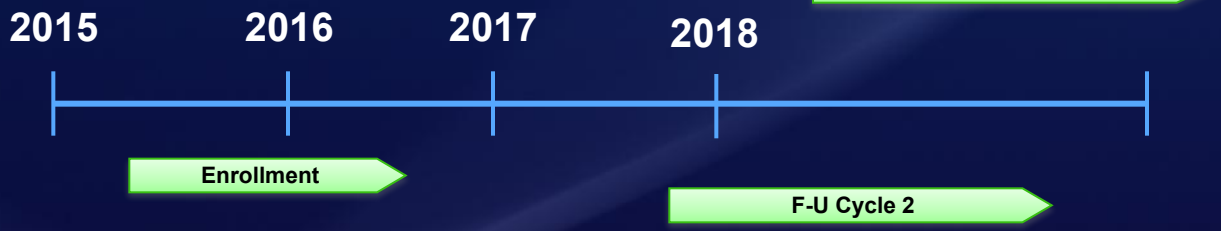
≥70 Years Old



50-69 Years Old



30-49 Years Old



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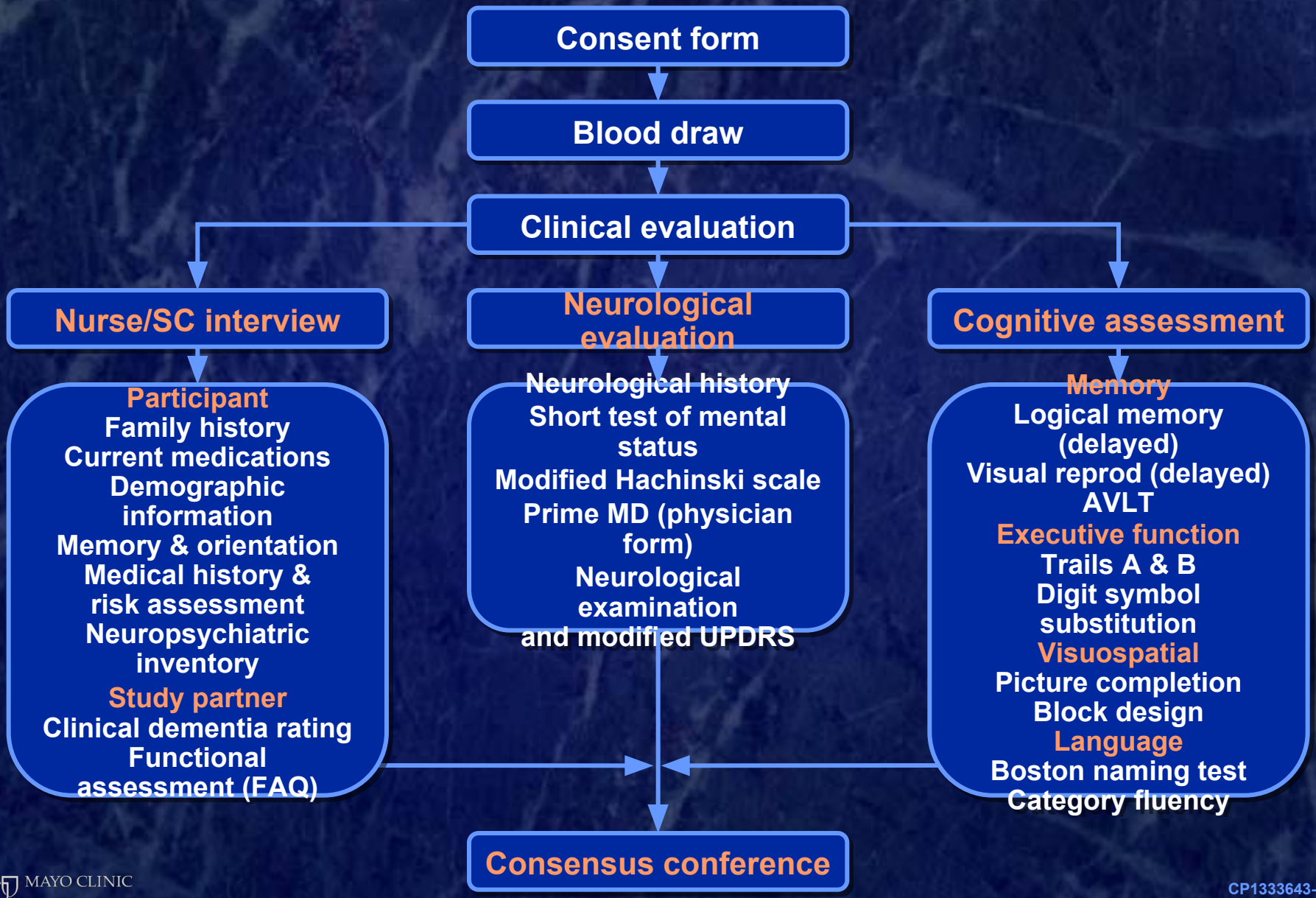
Evaluation


Consent form
Blood draw
Clinical evaluation
Nurse/SC interview
Neurological evaluation
Cognitive assessment
Participant
Family history
Current medications
Demographic information
Memory & orientation
Medical history & risk assessment
Neuropsychiatric inventory
Study partner
Clinical dementia rating
Functional assessment (FAQ)
Neurological history
Short test of mental status
Modified Hachinski scale
Prime MD (physician form)
Neurological examination
and modified UPDRS
Memory
Logical memory (delayed)
Visual reprod (delayed)
AVLT
Executive function
Trails A & B
Digit symbol substitution
Visuospatial
Picture completion
Block design
Language
Boston naming test
Category fluency
Consensus conference

Resources Acquired

- 5000+ non-demented subjects
  - 80% Cognitively normal
  - 18% MCI
  - 2% Demented
- 5800 quantitative MRI scans
- ~ 5000 DNA samples
- ~ 5000 frozen plasma/serum samples plus annual samples
- Clinical and performance measures

Continuation of MCSA

- Add new subjects to cohort (500?)
- Continue annual clinical follow-ups
- Continue serial MRI/PET scans
- Collect annual plasma/serum
- Collected 1200 CSF's
- Performed 2800 FDG-PET scans
- Performed 2800 PiB PET scans
- Performed 1000 tau PET scans

Biomarker Behavior in the Population

Assessing Biomarkers in the Community

- **Biomarker negative (A- N-)**
  - Amyloid neg
  - FDG PET/MRI neg
- **Amyloid positive Neurodeg neg (A+ N-)**
  - Amyloid pos
  - FDG PET/MRI neg
- **Amyloid pos Neurodeg pos (A+ N+)**
  - Amyloid pos
  - FDG PET/MRI pos
- **Neurodegen only (A- N+) (SNAP)**
  - Amyloid neg
  - FDG PET/MRI pos

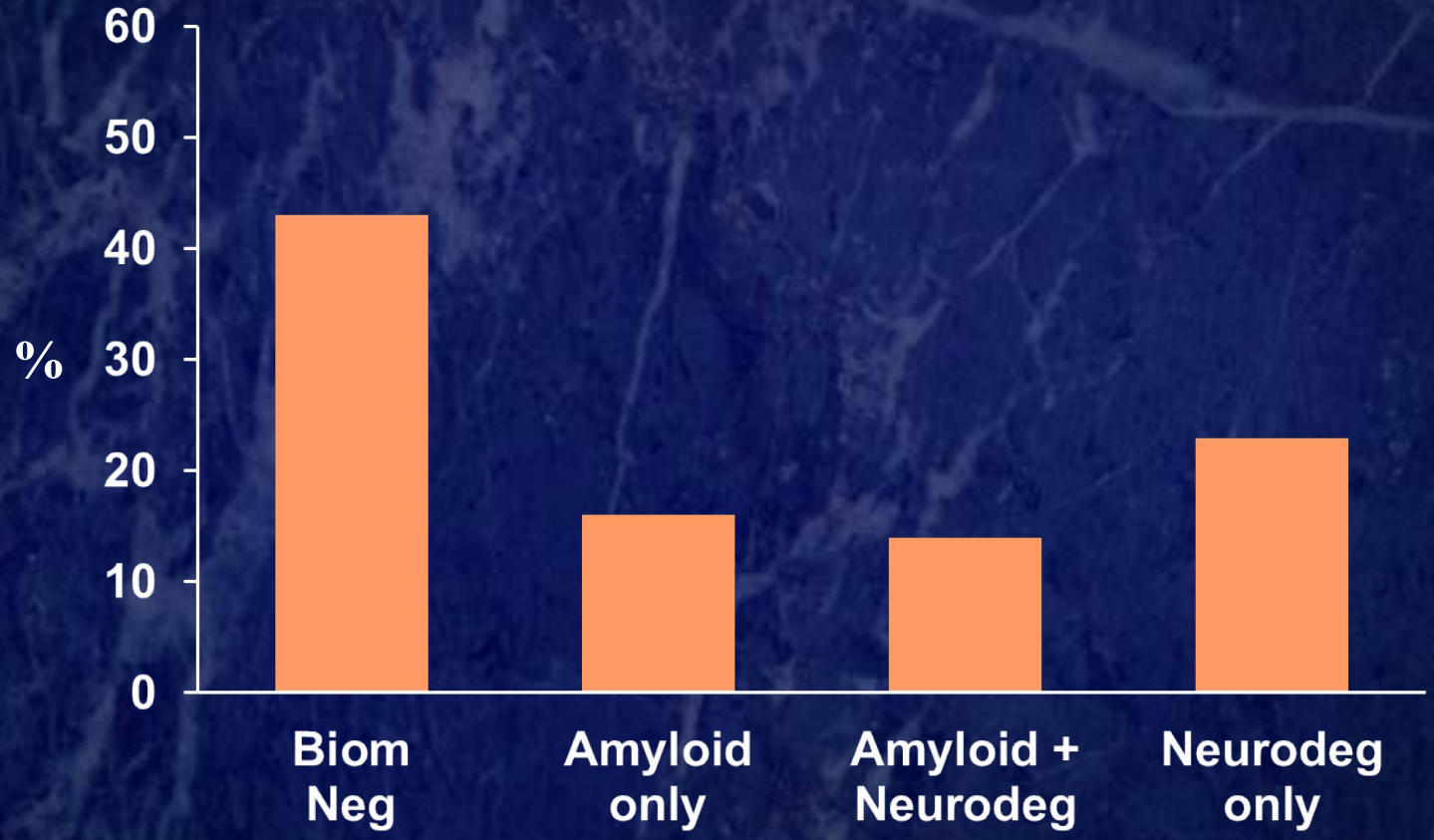
Preclinical AD

Preclinical AD

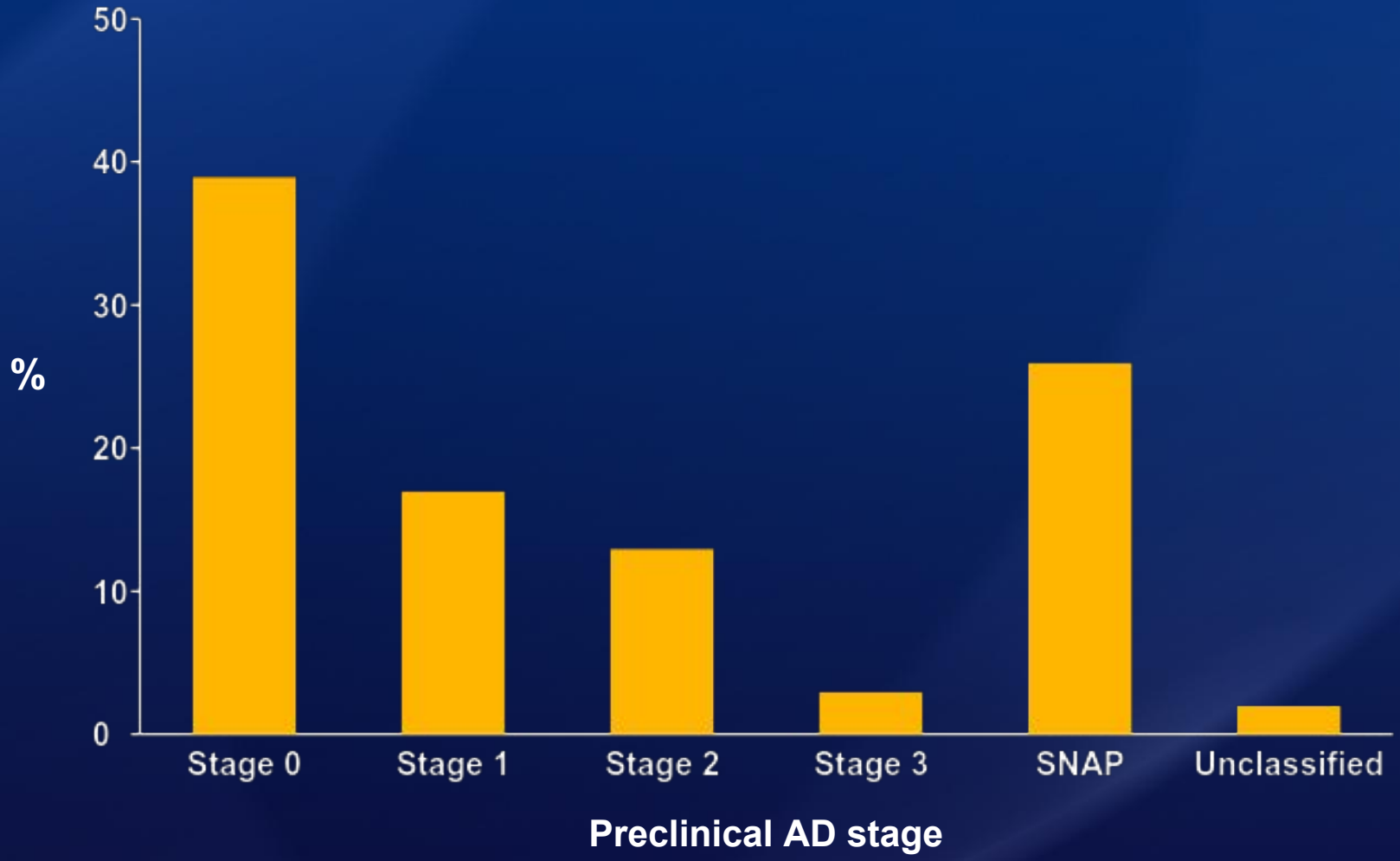
Diagnostic category	Aβ (PET or CSF)	Neuronal injury	Clinical
Stage 1	Positive	Negative	Negative
Stage 2	Positive	Positive	Negative
Stage 3	Positive	Positive	Positive
Stage 0	Negative	Negative	Negative

Sperling et al: 2011

Pre-clinical Normal
Population Frequencies
Jack et al., Ann Neurol, 2012



Preclinical Stage



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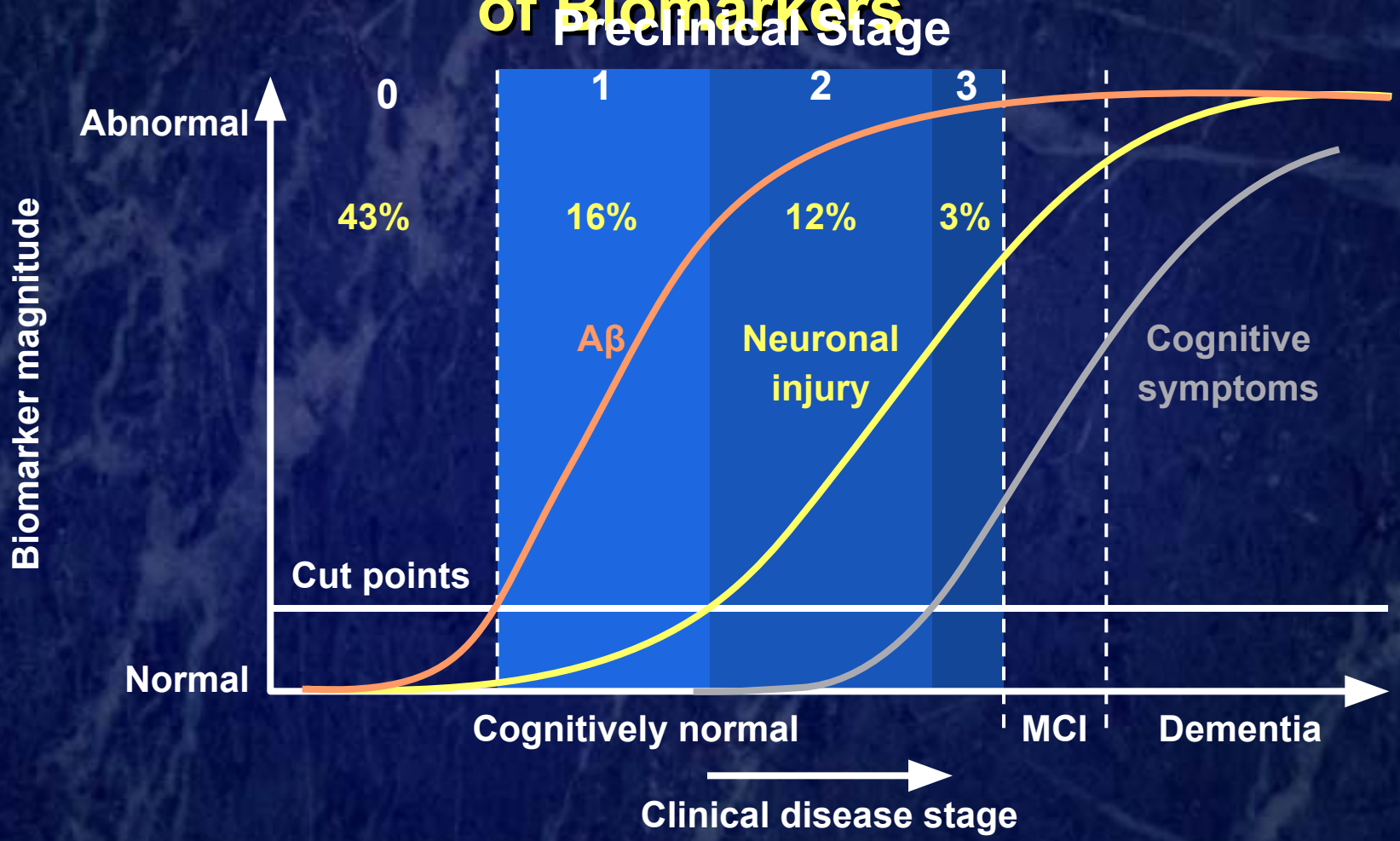
NIA-AA Preclinical AD Staging in Relation to Our Hypothetical Model of Biomarkers



Jack et al: Lancet Neuro, 2010

Biomarkers Across the Age Spectrum

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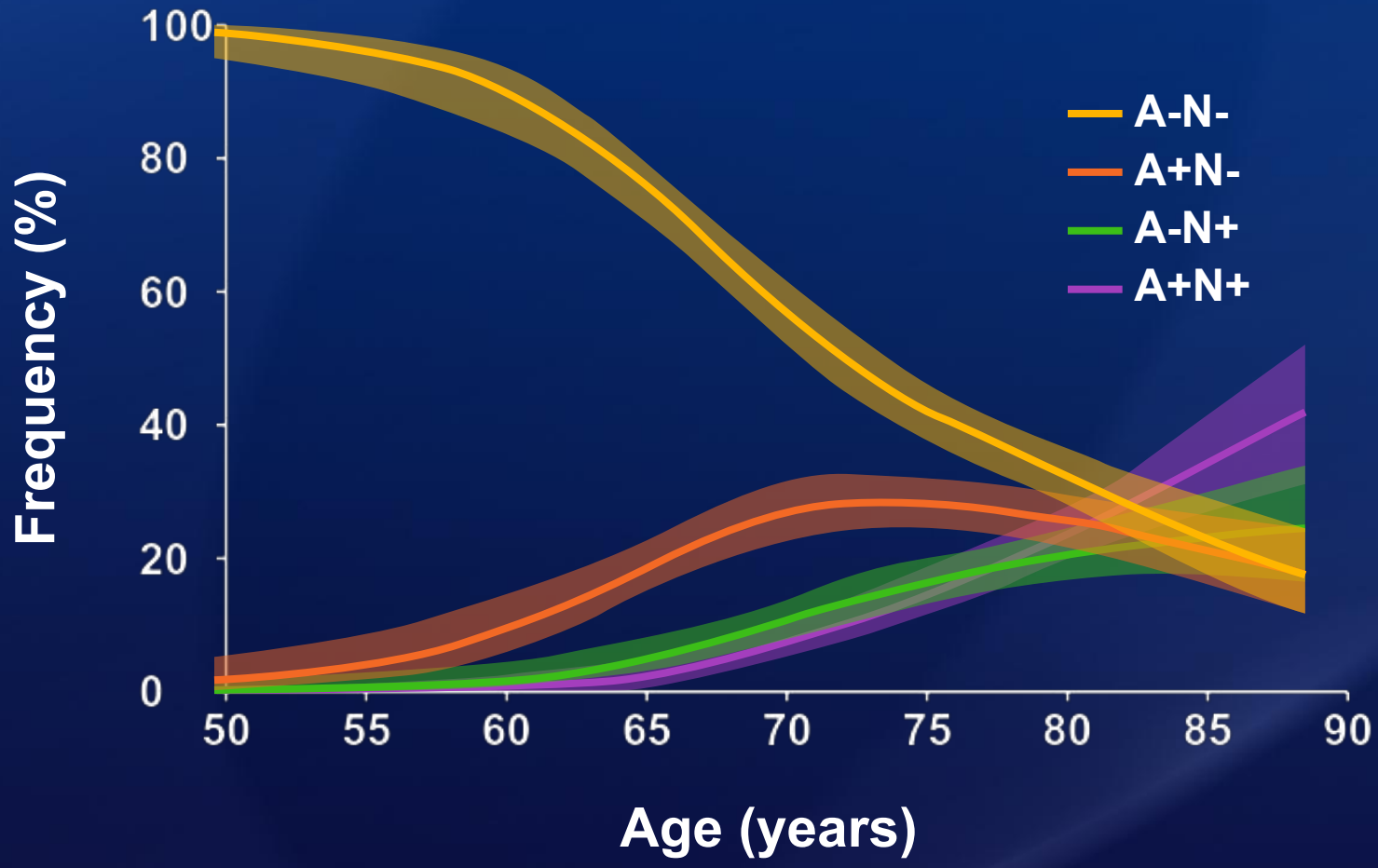
Assessing Biomarkers in the Community

- **Biomarker negative (A- N-)**
  - Amyloid neg
  - FDG PET/MRI neg
- **Amyloid positive Neurodeg neg (A+ N-)**
  - Amyloid pos
  - FDG PET/MRI neg
- **Amyloid pos Neurodeg pos (A+ N+)**
  - Amyloid pos
  - FDG PET/MRI pos
- **Neurodegen only (A- N+) (SNAP)**
  - Amyloid neg
  - FDG PET/MRI pos

Population Frequencies of Biomarkers in Typical AD



Jack et al: Lancet Neurol 13:997, 2014

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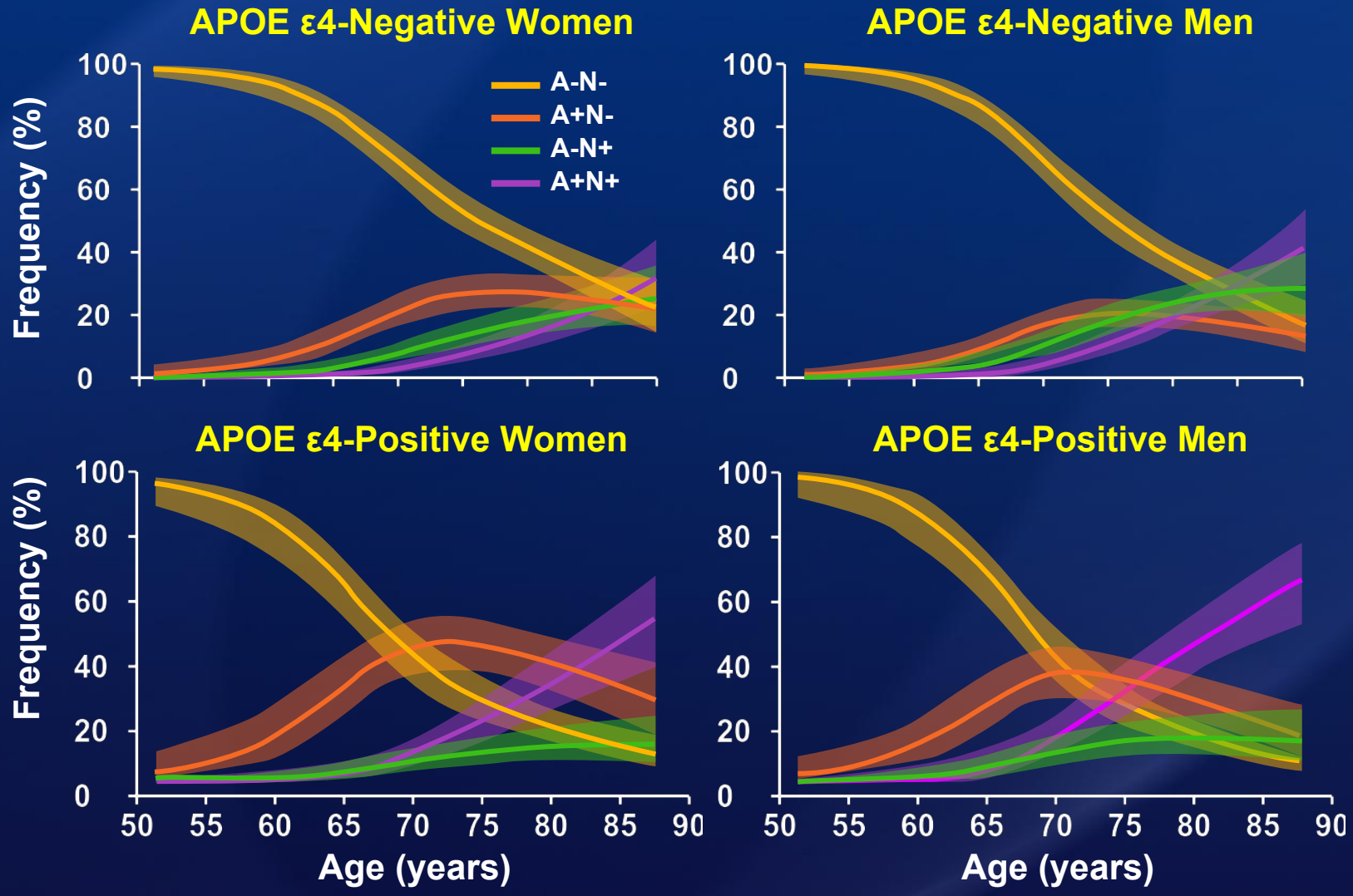
Population Frequencies of Biomarkers by Age, Sex and ApoE4 Status



Jack et al: Lancet Neurol 13:997, 2014

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Preclinical Alzheimer's Disease and Its Outcome: A Longitudinal Cohort Study

Stephanie J. B. Vos; Chengjie Xiong; Pieter Jelle Visser; Mateusz S. Jasielec; Jason Hassenstab; Elizabeth A. Grant; Nigel J. Cairns; John C. Morris; David M. Holtzman; Anne M. Fagan

Lancet Neurology, 12:957, Oct., 2013

Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study

Stephanie J B Vos, Chengjie Xiong, Pieter Jelle Visser, Mateusz S Jasielec, Jason Hassenstab, Elizabeth A Grant, Nigel J Cairns, John C Morris, David M Holtzman, Anne M Fagan

Summary

Background New research criteria for preclinical Alzheimer's disease have been proposed, which include stages for cognitively normal individuals with abnormal amyloid markers (stage 1), abnormal amyloid and neuronal injury markers (stage 2), or abnormal amyloid and neuronal injury markers and subtle cognitive changes (stage 3). We aimed to investigate the prevalence and long-term outcome of preclinical Alzheimer's disease according to these criteria.

Methods Participants were cognitively normal (clinical dementia rating [CDR]=0) community-dwelling volunteers aged at least 65 years who were enrolled between 1998 and 2011 at the Washington University School of Medicine (MO, USA). CSF amyloid-β_{1-42} and tau concentrations and a memory composite score were used to classify participants as normal (both markers normal), preclinical Alzheimer's disease stage 1–3, or suspected non-Alzheimer pathophysiology (SNAP, abnormal injury marker without abnormal amyloid marker). The primary outcome was the proportion of participants in each preclinical AD stage. Secondary outcomes included progression to CDR at least 0·5, symptomatic Alzheimer's disease (score of at least 0·5 for memory and at least one other domain and cognitive impairments deemed to be due to Alzheimer's disease), and mortality. We undertook survival analyses using subdistribution and standard Cox hazards models and linear mixed models.

Findings Of 311 participants, 129 (41%) were classed as normal, 47 (15%) as stage 1, 36 (12%) as stage 2, 13 (4%) as stage 3, 72 (23%) as SNAP, and 14 (5%) remained unclassified. The 5-year progression rate to CDR at least 0·5, symptomatic Alzheimer's disease was 2% for participants classed as normal, 11% for stage 1, 26% for stage 2, 56% for stage 3, and 5% for SNAP. Compared with individuals classed as normal, participants with preclinical Alzheimer's disease had an increased risk of death after adjusting for covariates (hazard ratio 6·2, 95% CI 1·1–35·0; p=0·040).

Interpretation Preclinical Alzheimer's disease is common in cognitively normal elderly people and is associated with future cognitive decline and mortality. Thus, preclinical Alzheimer's disease could be an important target for therapeutic intervention.

Funding National Institute of Aging of the National Institutes of Health (P01-AG003991, P50-AG05681, P01-AG02676), Internationale Stichting Alzheimer Onderzoek, the Center for Translational Molecular Medicine project LeARN, the EU/EFPIA Innovative Medicines Initiative Joint Undertaking, and the Charles and Joanne Knight Alzheimer Research Initiative.

Introduction

Alzheimer's disease (AD) starts with a preclinical phase in which AD neuropathological abnormalities begin to accumulate but cognitive ability is normal.[1–3] Now that biomarkers for AD have become available, identification of preclinical AD in vivo in cognitively normal individuals is possible.[4] Information regarding the occurrence and outcome of preclinical AD is crucial for the understanding of AD pathophysiology and the design of secondary prevention trials.

Research criteria for preclinical AD have been proposed by the Preclinical Working Group of the National Institute on Aging (NIA) and Alzheimer's Association (AA).[5] The NIA-AA criteria for preclinical AD propose ordered stages for cognitively normal individuals with abnormal amyloid markers (stage 1), abnormal amyloid and neuronal injury markers (stage 2), and abnormal amyloid and neuronal injury markers and subtle cognitive changes (stage 3).[5] In a 2012 study in which structural and amyloid imaging markers were used to categorise individuals according to these stages,[6] the rate of short-term (1 year) progression to mild cognitive impairment (MCI) or dementia increased with advancing preclinical AD stage.

The aim of this study was to identify the prevalence and long-term outcome of preclinical AD according to these criteria in a cohort of cognitively normal individuals. We used CSF markers to define NIA-AA preclinical AD stages and assessed the long-term cognitive and mortality outcomes of participants in each stage. We also tested whether the proportion and cognitive outcome of preclinical AD were affected by age or *APOE* genotype.

Methods

Participants

Participants were cognitively normal community-dwelling volunteers enrolled between June, 1998, and September, 2011, in longitudinal studies of memory and

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See **Comment** page 933

Department of Psychiatry and Neuropsychology, Maastricht University, School for Mental Health and Neuroscience, Alzheimer Center Limburg, Maastricht, Netherlands (S J B Vos MSc, P J Visser MD); **Division of Biostatistics** (Prof C Xiong PhD, M S Jasielec MS, E A Grant PhD), **The Knight Alzheimer's Disease Research Center** (Prof C Xiong, J Hassenstab PhD, E A Grant, Prof N J Cairns PhD, Prof J C Morris MD, Prof D M Holtzman MD, Prof A M Fagan PhD), **Department of Psychology** (J Hassenstab), **Department of Neurology** (Prof N J Cairns, Prof J C Morris, Prof D M Holtzman, Prof A M Fagan), **Department of Pathology and Immunology** (Prof N J Cairns, Prof J C Morris), **and Hope Center for Neurological Disorders** (Prof D M Holtzman, Prof A M Fagan), **Washington University School of Medicine, St Louis, MO, USA; and Alzheimer Center and Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, Netherlands** (P J Visser)

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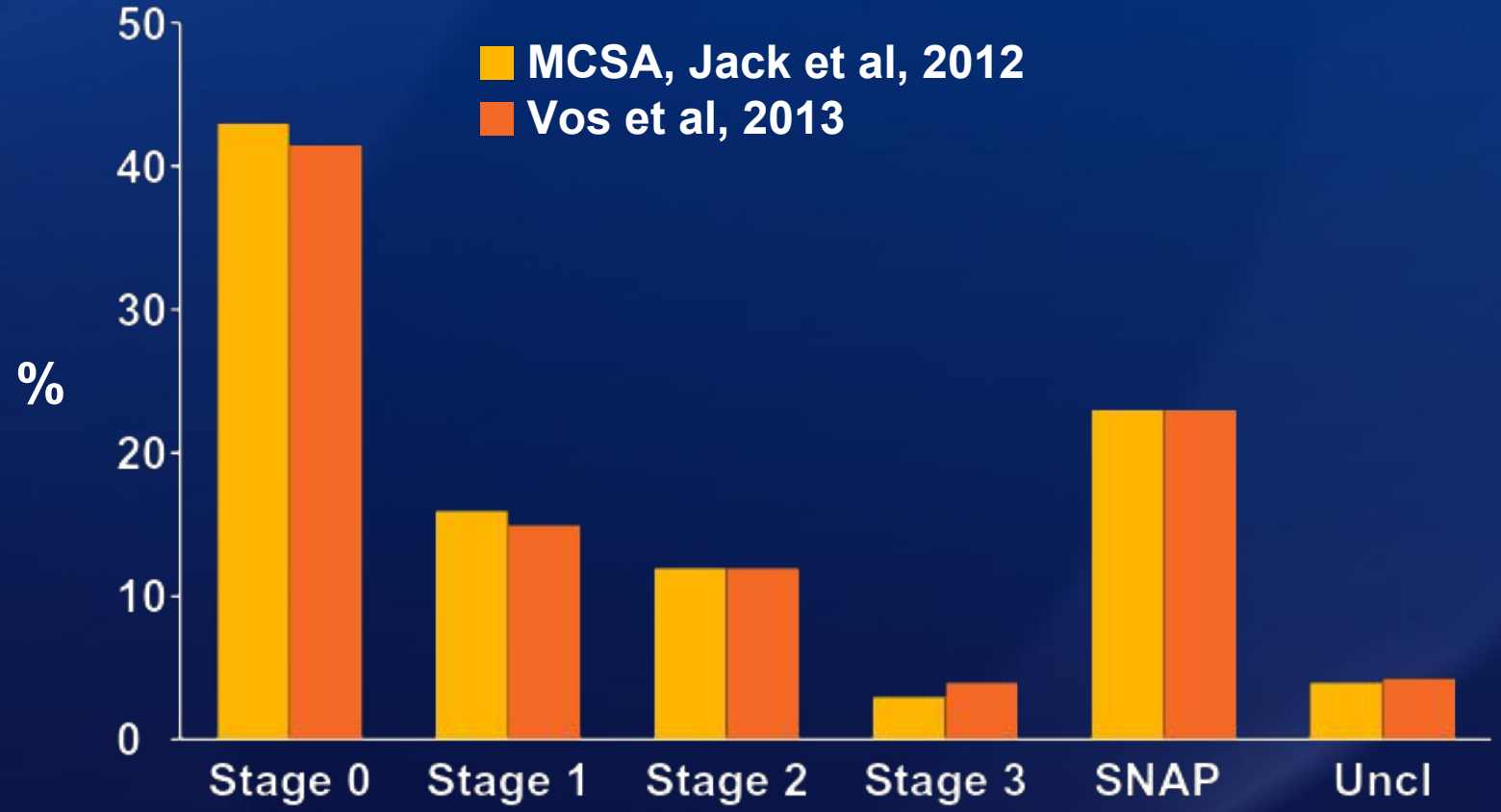
Pre-Clinical AD Stages
Neuroimaging vs CSF



Petersen: Lancet Neurol, 2013

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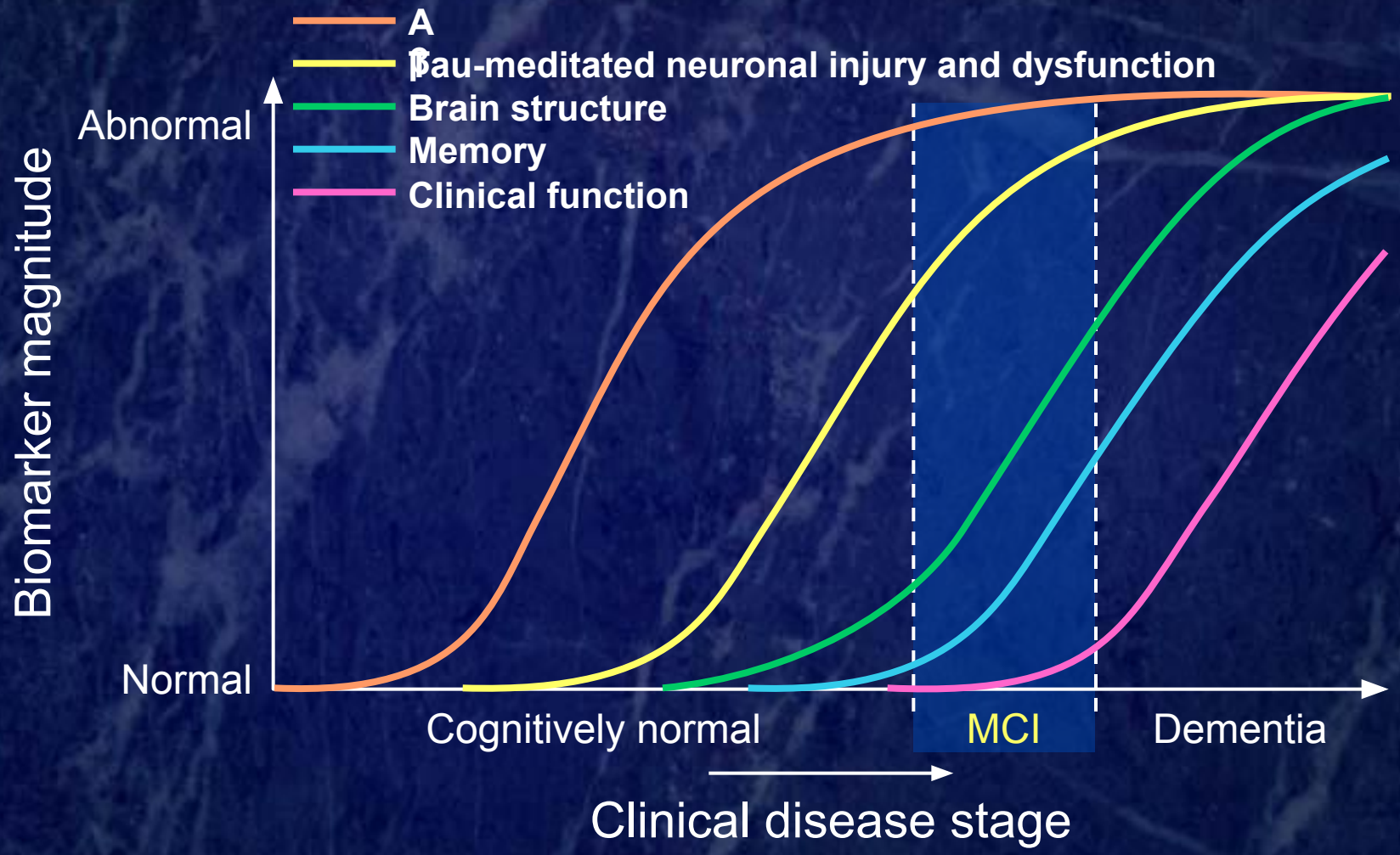
MCI Due to AD

Hypothetical Model of Dynamic Biomarkers of the Alzheimer's Pathological Cascade



Jack et al: Lancet Neurol 2010

MCI Due to AD

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (tau, FDG, sMRI)
MCI	Uninformative	Conflicting/ indeterminant or unavailable	
MCI due to AD – intermediate likelihood	Intermediate 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: 2011

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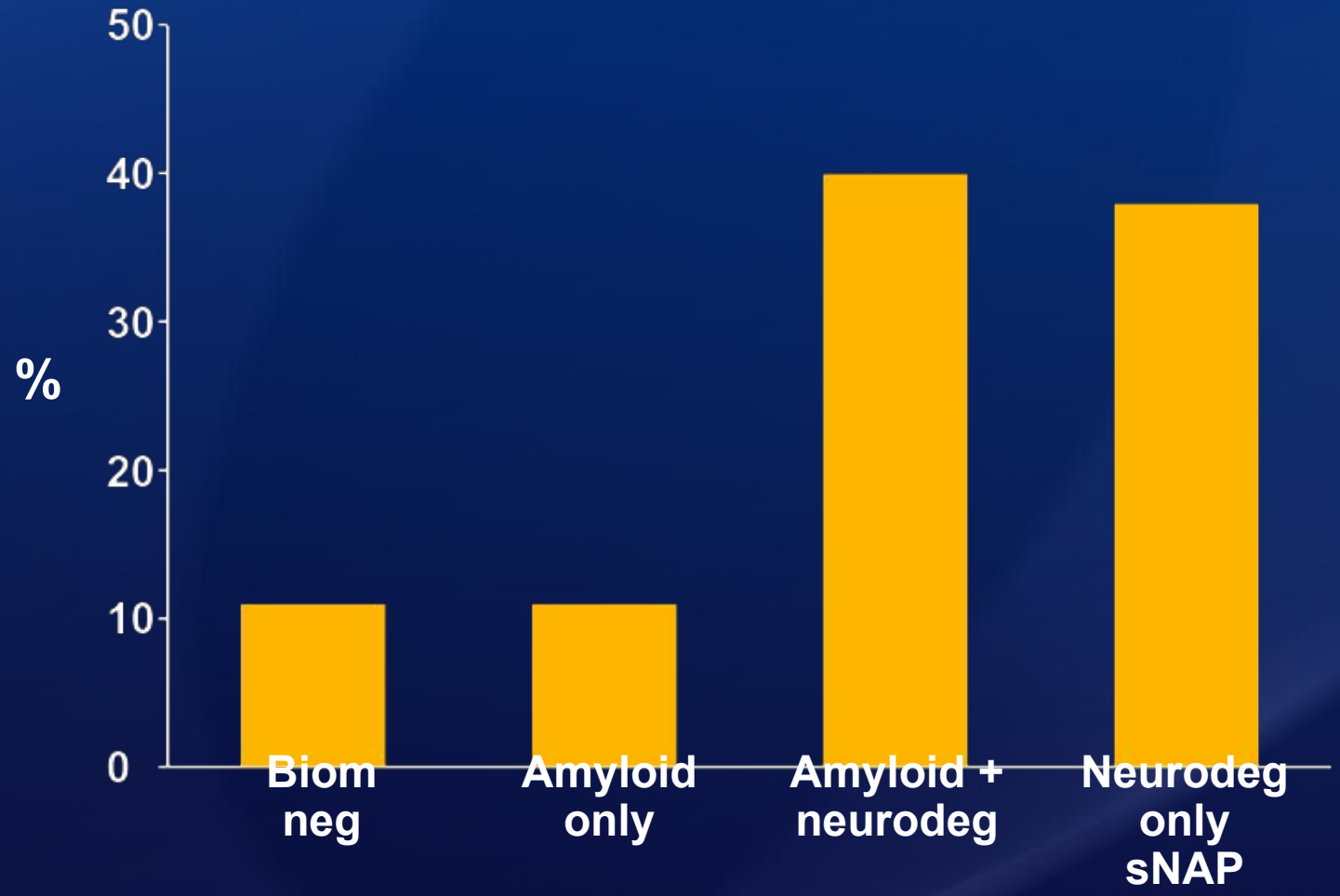
All MCI MCSA
Population Frequencies



Petersen et al: Ann Neuro , 2013

But…

Life is not simple

Amyloid/Tau/Neurodegeneration

a descriptive classification scheme for AD biomarkers

Adding Tau as a Biomarker

A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers

OPEN

Clifford R. Jack, Jr., MD
David A. Bennett, MD
Kaj Blennow, MD, PhD
Maria C. Carrillo, PhD
Howard Feldman, MD
Giovanni B. Frisoni, MD
Harald Hampel, MD, PhD
William Jagust, MD
Keith A. Johnson, MD
David S. Knopman, MD
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Bruno Dubois, MD, PhD

ABSTRACT

Biomarkers have become an essential component of Alzheimer disease (AD) research and because of the pervasiveness of AD pathology in the elderly, the same biomarkers are used in cognitive aging research. A number of current issues suggest that an unbiased descriptive classification scheme for these biomarkers would be useful. We propose the "A/T/N" system in which 7 major AD biomarkers are divided into 3 binary categories based on the nature of the pathophysiology that each measures. "A" refers to the value of a β-amyloid biomarker (amyloid PET or CSF $A\beta_{42}$); "T," the value of a tau biomarker (CSF phospho tau, or tau PET); and "N," biomarkers of neurodegeneration or neuronal injury ([^{18}F]-fluorodeoxyglucose–PET, structural MRI, or CSF total tau). Each biomarker category is rated as positive or negative. An individual score might appear as A+/T+/N−, or A+/T−/N−, etc. The A/T/N system includes the new modality tau PET. It is agnostic to the temporal ordering of mechanisms underlying AD pathogenesis. It includes all individuals in any population regardless of the mix of biomarker findings and therefore is suited to population studies of cognitive aging. It does not specify disease labels and thus is not a diagnostic classification system. It is a descriptive system for categorizing multidomain biomarker findings at the individual person level in a format that is easy to understand and use. Given the present lack of consensus among AD specialists on terminology across the clinically normal to dementia spectrum, a biomarker classification scheme will have broadest acceptance if it is independent from any one clinically defined diagnostic scheme. *Neurology*® 2016;87:1-9

ATN Biomarker Grouping

- B-amyloid plaques (A)
  - CSF Ab 42 (low), or better low 42/40 ratio
  - Amyloid PET
- Aggregated tau (T)
  - CSF phosphorylated tau (high)
  - Tau PET
- Neuronal injury and neurodegeneration (N)
  - Structural MRI
  - FDG PET
  - CSF total tau (high)

A/T/N for MCI

A/T/N score	NIA-AA classification	2014 IWG classification
A-/T-/N-	MCI – unlikely due to AD	Not defined
A+/T-/N-	MCI – core clinical criteria*	Typical AD (if A+ established by amyloid PET)
A+/T+/N-	MCI – core clinical criteria*	Typical AD
A+/T-/N+	MCI – core clinical criteria*	Typical AD (if A+ established by amyloid PET)
A+/T+/N+	MCI due to AD – high likelihood	Typical AD
A-/T+/N- **	Not defined	Not defined
A-/T-/N+ **	Not defined	Not defined
A-/T+/N+ **	Not defined	Not defined

*In event of conflicting results, biomarkers are regarded as "uninformative" and therefore do not alter the individual's diagnostic classification based on clinical assessment alone

** Described as MCI-SNAP in several publications

Jack et al: Neurology in press

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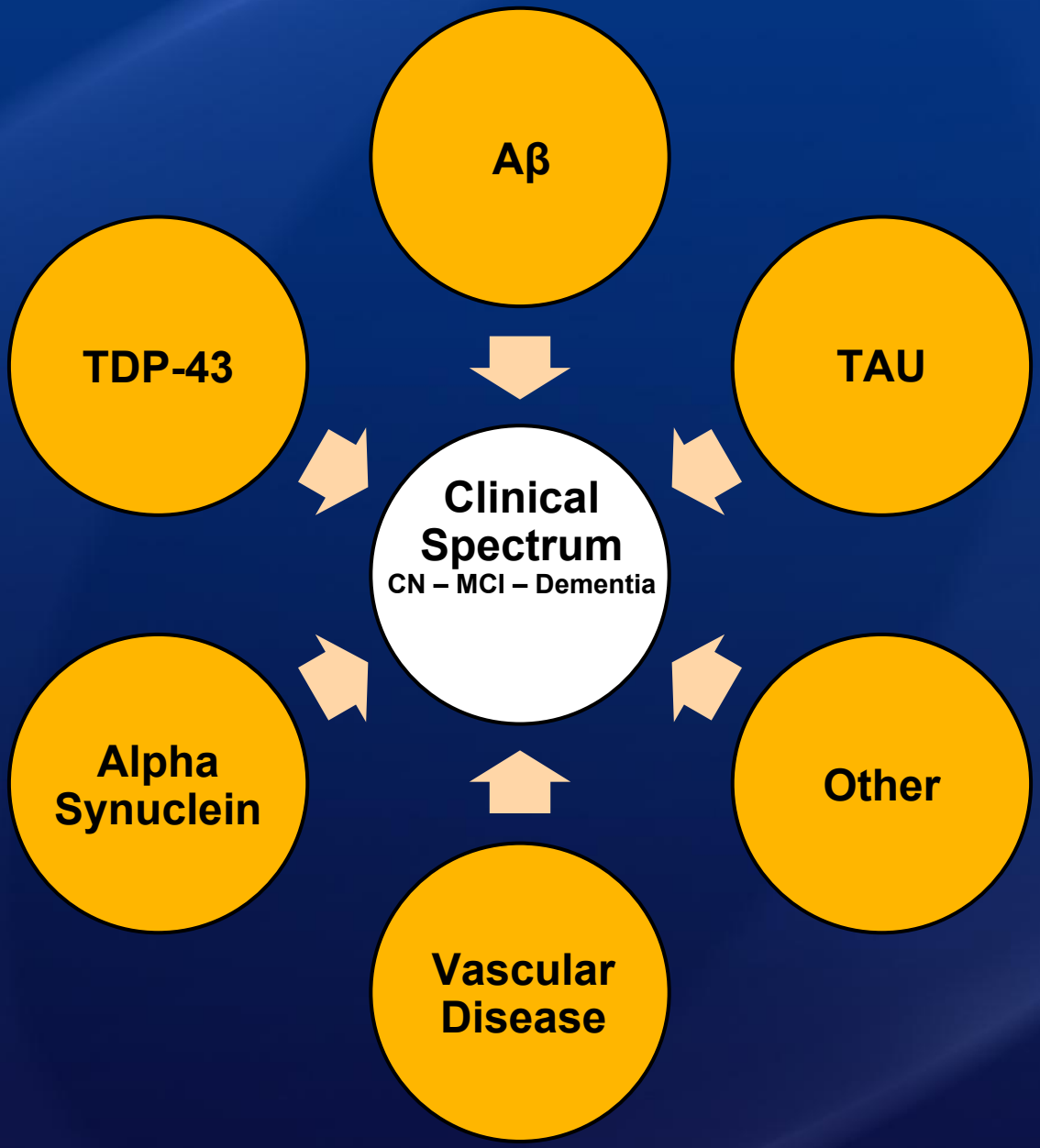
Summary: ATN

- Descriptive system for categorizing multi-domain biomarker
- Includes tau PET
- Includes all individuals in population
- Applicable to any clinical classification system
- Allows investigators to communicate in a common language
- Unifying conceptual approach to biomarkers

But, at the end of the day…

MAYO CLINIC



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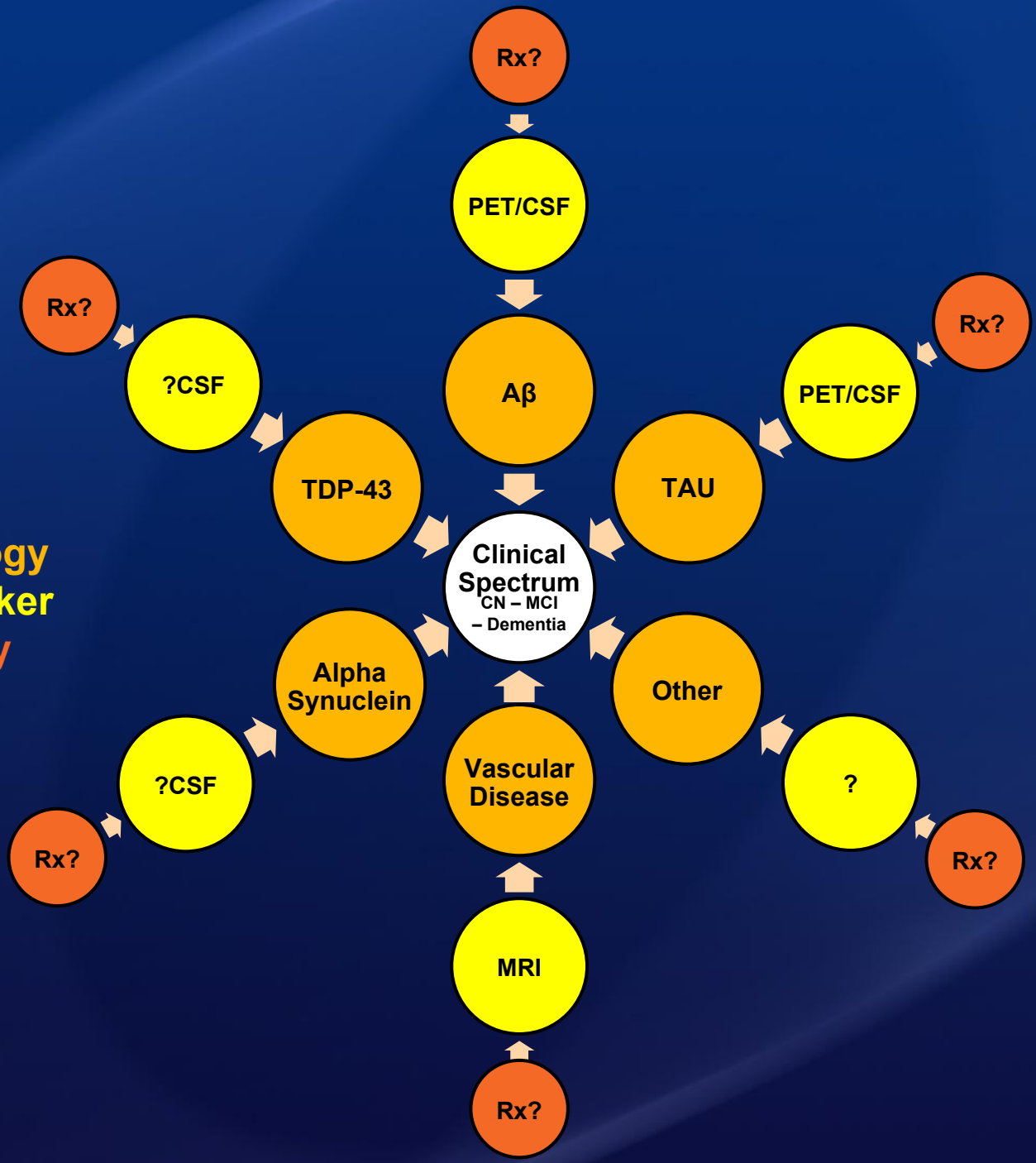

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Thank You