The Changing Landscape of Alzheimer's Disease

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EVMS

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Disclosures

- Roche, Inc.
- Merck, Inc.
- Genentech, Inc.
- Biogen, Inc.
- Eisai, Inc.

- National Institute on Aging:
  - U01 AG006786
  - P50 AG016574
  - U01 AG011378
  - R01 AG011378
  - R01 AG041581
  - GHR Foundation
  - Mayo Foundation for Education and Research

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What is a biomarker?

- A measure of brain pathology that can be obtained in the living subject – biomarkers are proxies for specific pathological changes in the brain
- Accepted Alzheimer's biomarkers are imaging or biofluids (CSF)

Outline

- AD Diagnosis past and current
- ATN Framework
- Mayo Clinic Study of Aging
- Biomarkers in the community
- Big picture and future directions

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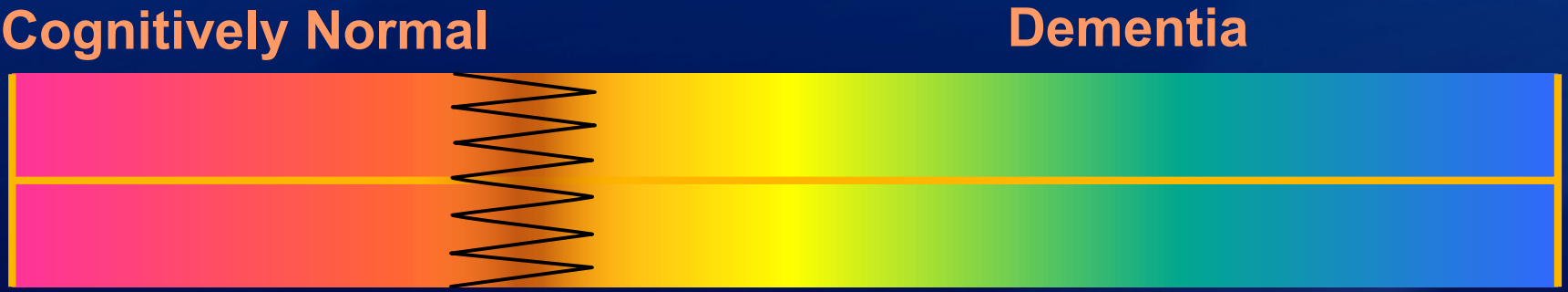
Old Conception of Alzheimer's Disease



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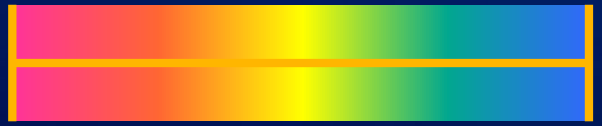
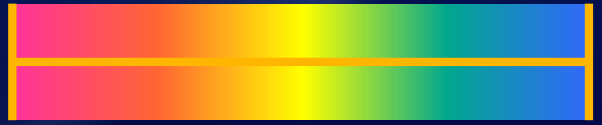
Alzheimer's Disease Spectrum

Preclinical AD

MCI Due to AD



Dementia Due to AD



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NINCDS-ADRDA Criteria 1984

views &reviews

Article abstract—Clinical criteria for the diagnosis of Alzheimer's disease include insidious onset and progressive impairment of memory and other cognitive functions. There are no motor, sensory, or coordination deficits early in the disease. The diagnosis cannot be determined by laboratory tests. These tests are important primarily in identifying other possible causes of dementia that must be excluded before the diagnosis of Alzheimer's disease may be made with confidence. Neuropsychological tests provide confirmatory evidence of the diagnosis of dementia and help to assess the course and response to therapy. The criteria proposed are intended to serve as a guide for the diagnosis of probable, possible, and definite Alzheimer's disease; these criteria will be revised as more definitive information becomes available.

Clinical diagnosis of Alzheimer's disease:

Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease

Guy McKhann, MD; David Drachman, MD; Marshall Folstein, MD; Robert Katzman, MD; Donald Price, MD; and Emanuel M. Stadlan, MD

Alzheimer's disease is a brain disorder characterized by a progressive dementia that occurs in middle or late life. The pathologic characteristics are degeneration of specific nerve cells, presence of neuritic plaques, and neurofibrillary tangles. Alterations in transmitter-specific markers include forebrain cholinergic systems, and, in some cases, noradrenergic and somatostatinergic systems that innervate the telencephalon.

A Work Group on the Diagnosis of Alzheimer's Disease was established by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA). The group intended to establish and to describe clinical criteria for the diagnosis of Alzheimer's disease of particular importance for research protocols and to describe approaches that would be useful for assessing the natural history of the disease. The need to refine clinical diagnostic criteria has been emphasized because 20% or more of cases with the clinical diagnosis of Alzheimer's disease are found at autopsy to have other conditions and not Alzheimer's disease. Moreover, therapeutic trials can be meaningfully compared only if uniform criteria are used for diagnosis and response to treatment.

The need for this report was suggested by the National Advisory Council of the NINCDS. The report has been reviewed by workshop participants, representatives of the National Advisory Neurological and Communicative Disorders and Stroke Council, representatives of the ADRDA, and designated reviewers representing professional societies concerned with the diagnosis of Alzheimer's disease. (For list of professional societies and designated reviewers, see page 943.)

The report was developed by subgroups that addressed medical history, clinical examination, neuropsychological testing, and laboratory assessments; the report was then discussed in plenary session. Based on a consensus of the participants, criteria were developed to serve as a clinical basis for diagnosis. These criteria should be useful also for comparative studies of patients in different kinds of investigations, including case control studies, therapeutic trials, evaluation of new diagnostic laboratory tests, and clinicopathologic correlations.

The criteria are not yet fully operational because of insufficient knowledge about the disease. The criteria are compatible with definitions in the current Diagnostic and Statistical Manual of Mental Disorders (DSM III) and in the International Classification of Diseases. These criteria must be regarded as tentative and subject to change. Additional longitudinal studies, confirmed by autopsy, are necessary to establish the validity of these criteria in com-

*For Work Group Participants and Affiliations, see page 943.

Accepted for publication March 20, 1984.

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Alzheimer's Disease as a Clinical – Pathological Entity

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Alzheimer's Disease

1984

NINCDS-ADRDA Criteria

Clinical-Pathological definition

↓

2011

NIA-AA Criteria

Clinical syndrome with biomarkers for amyloid and neurodegeneration

↓

2018

NIA-AA Framework

Alzheimer's disease as a biological entity
defined by positive biomarkers for amyloid and tau

Clinical Spectra Independent

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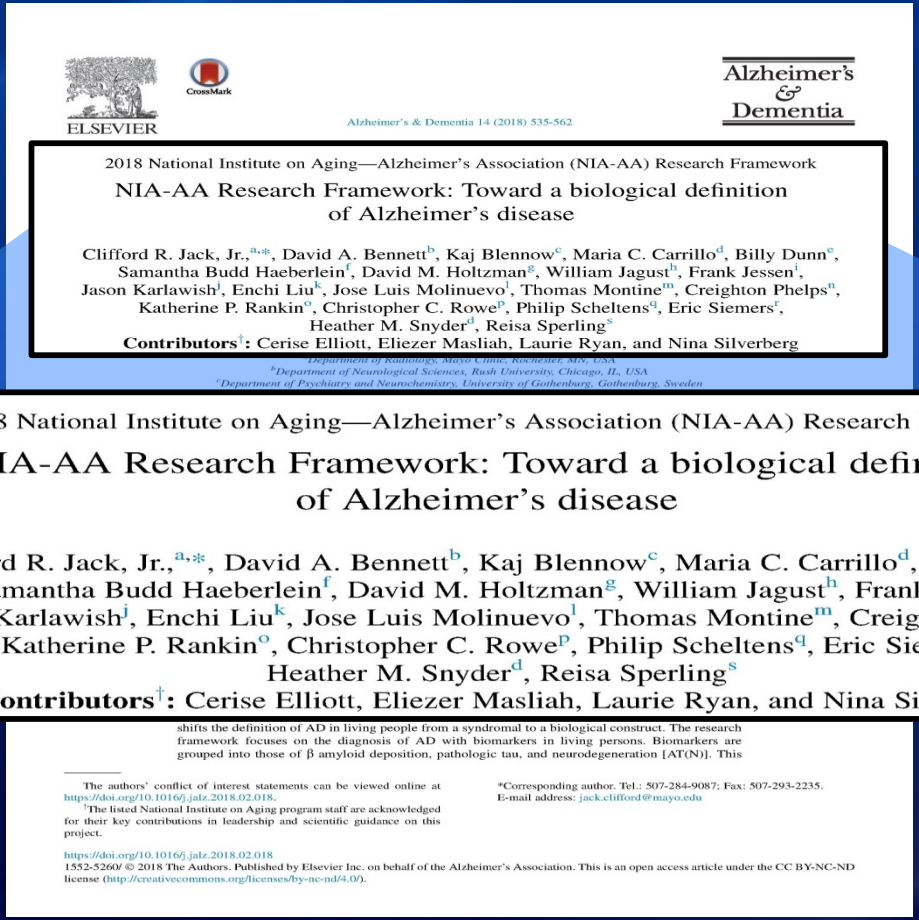

ELSEVIER

CrossMark

Alzheimer's & Dementia 14 (2018) 535-562

Alzheimer's & Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]

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2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

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shifts the definition of AD in living people from a syndromal to a biological construct. The research framework focuses on the diagnosis of AD with biomarkers in living persons. Biomarkers are grouped into those of β amyloid deposition, pathologic tau, and neurodegeneration [AT(N)]. This

The authors' conflict of interest statements can be viewed online at https://doi.org/10.1016/j.jalz.2018.02.018.

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Jack et al: Alzheimer's & Dementia 14(2018)535-562.

Outline

- AD Diagnosis past and current
- **ATN Framework**
- Mayo Clinic Study of Aging
- Biomarkers in the community
- Big picture and future directions

MAYO CLINIC

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

OPEN

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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)

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2018 NIA-AA Research Framework to Investigate the Alzheimer's Disease Continuum

Objective: update a scheme for *defining* and *staging* the disease across its entire spectrum with which the *research* community can communicate findings in a common manner

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What is the definition of AD?

- Term AD refers to pathologic change – not specific syndrome
- AD is identified at post mortem by pathologic changes and/or in vivo by biomarkers
  - Symptoms are part of the disease continuum not its definition
- **Major shift in thinking**

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Biomarker Profiles and Categories

ATN profiles	Biomarker category	
A-T-N-	Normal AD biomarkers	
A+T-N-	Alzheimer's pathologic change	Alzheimer's continuum
A+T-N+	Alzheimers pathologic change	
A+T+N-	Alzheimers disease	
A+T+N+	Alzheimers disease	
A-T+N-	Non- AD pathologic change	
A-T-N+	Non- AD pathologic change	
A-T+N+	Non- AD pathologic change	

If an individual has an abnormal amyloid biomarker study, but a biomarker for tau is not available, then the individual is placed into the "Alzheimer's continuum"

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Biomarker Profiles and Categories

A+T-N-	Alzheimer's pathologic change	Alzheimer's continuum
A+T-N+	Alzheimers pathologic change	
A+T+N-	Alzheimers disease	
A+T+N+	Alzheimers disease	

If an individual has an abnormal amyloid biomarker study, but a biomarker for tau is not available, then the individual is placed into the "Alzheimer's continuum"

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Biomarker Profiles and Categories

A+T+N-	Alzheimers disease
A+T+N+	Alzheimers disease

If an individual has an abnormal amyloid biomarker study, but a biomarker for tau is not available, then the individual is placed into the "Alzheimer's continuum"

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Neuroimaging in AD

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Amyloid Imaging

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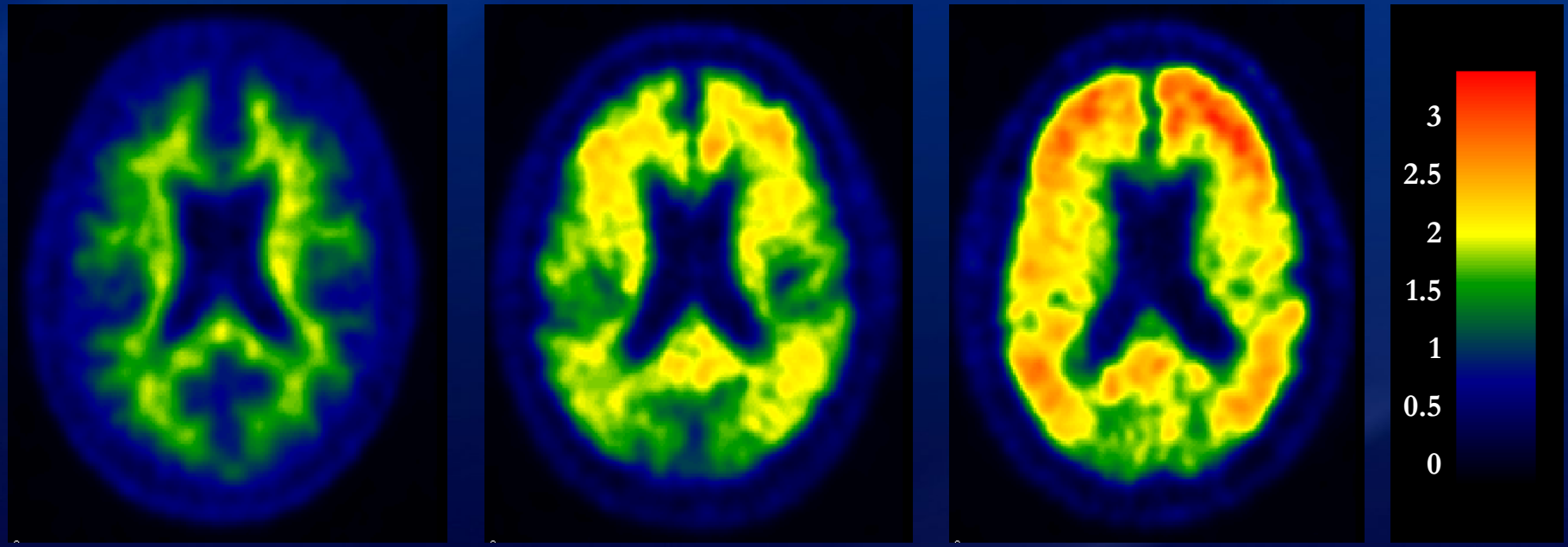
PIB Idealized

CN

aMCI

AD



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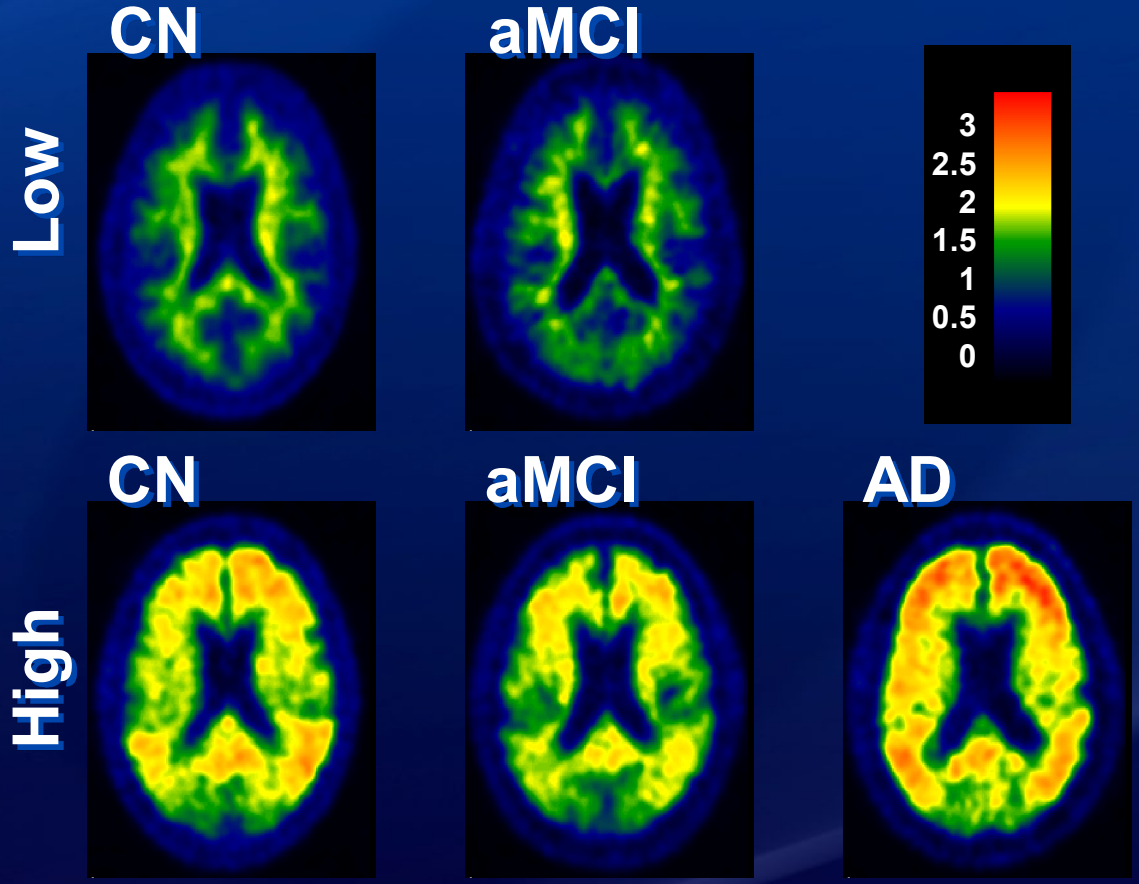
Amyloid PET – Full Spectrum



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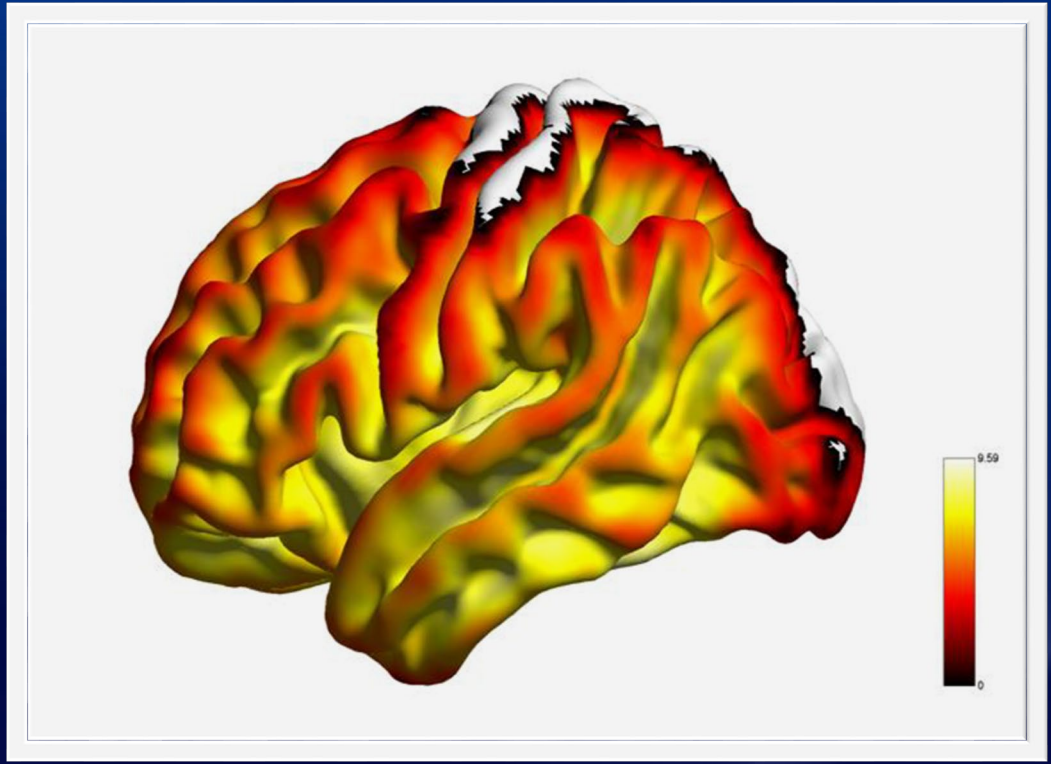
Amyloid (PiB) PET Differences
Cognitively Normal vs. AD Dementia



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Tau Imaging

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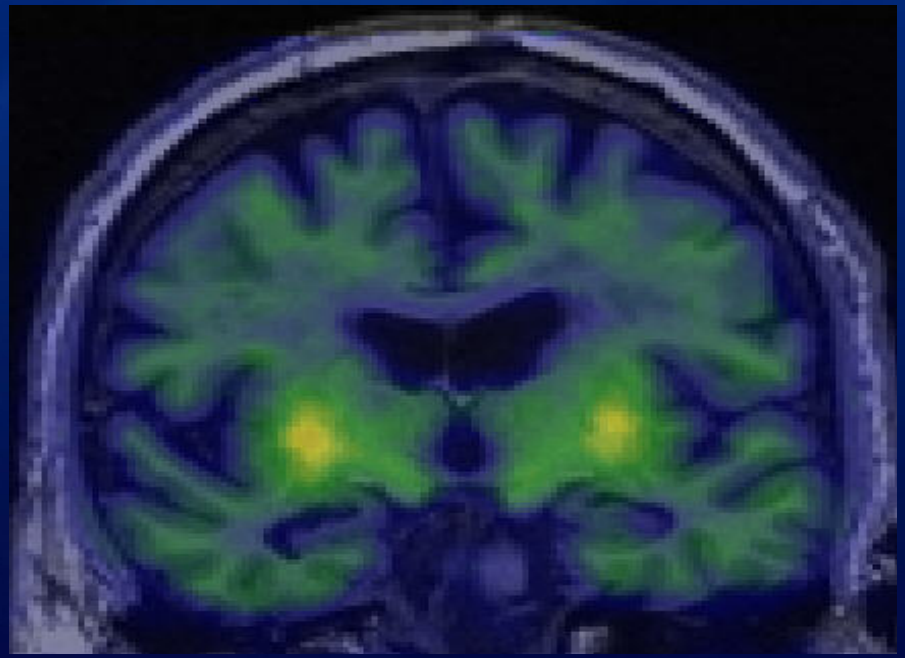
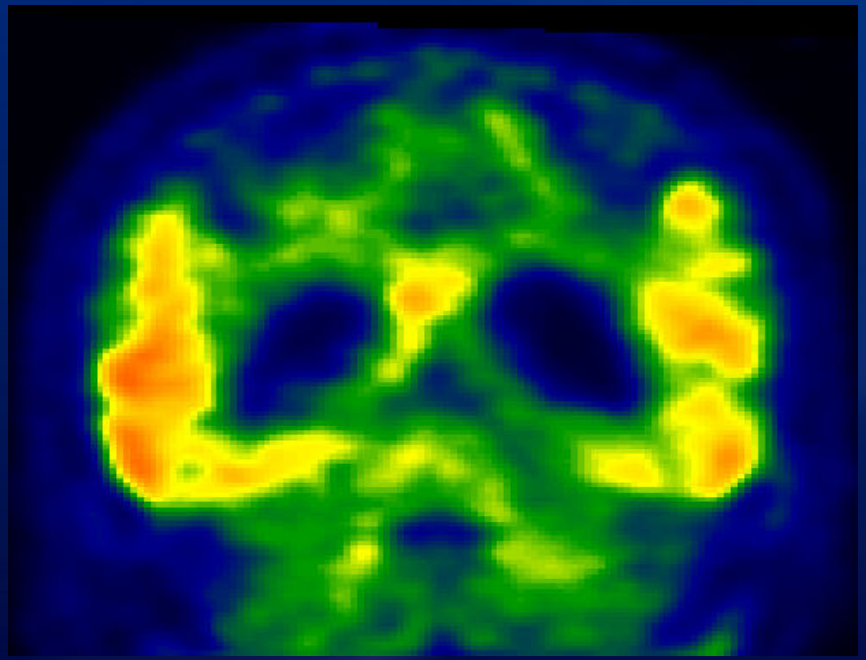
Tau PET

Clinically normal 84-yo



AD dementia 71-yo



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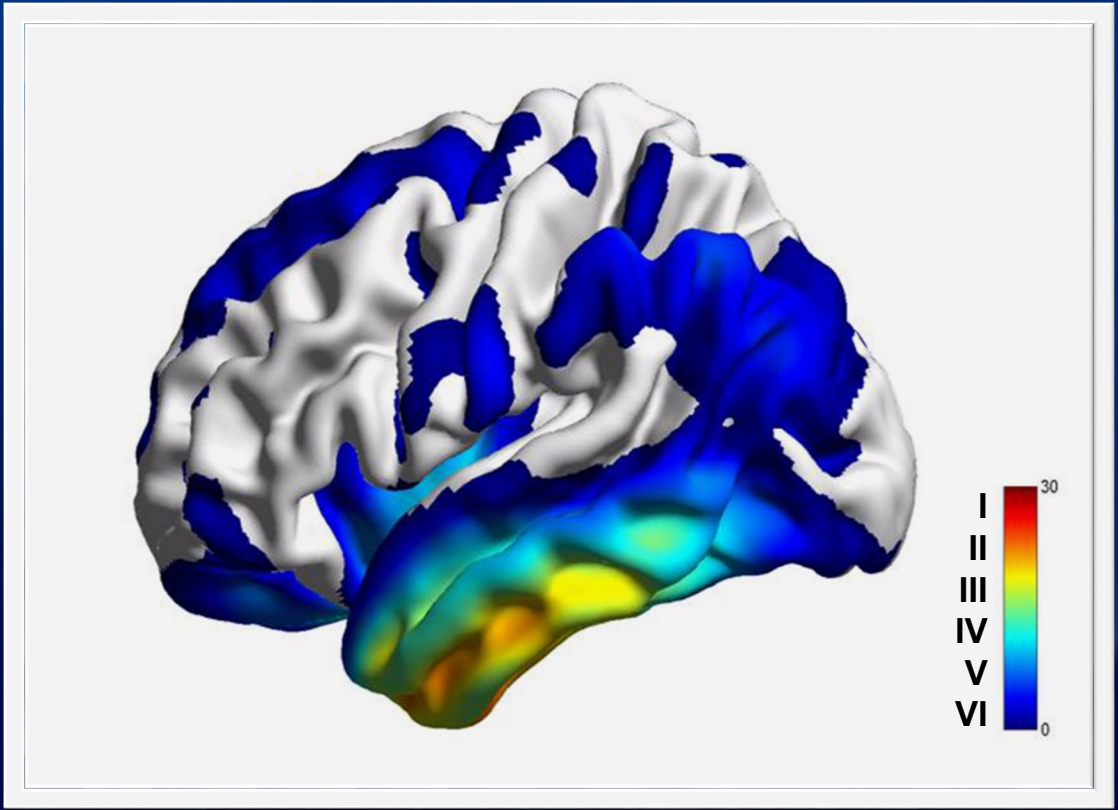
Tau PET
Cognitively Normal vs. AD Dementia



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Proposal to Define and Stage AD

To Stage AD

Neurodegeneration

MRI

FDG PET

Clinical Syndromes

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MRI Atrophy Patterns

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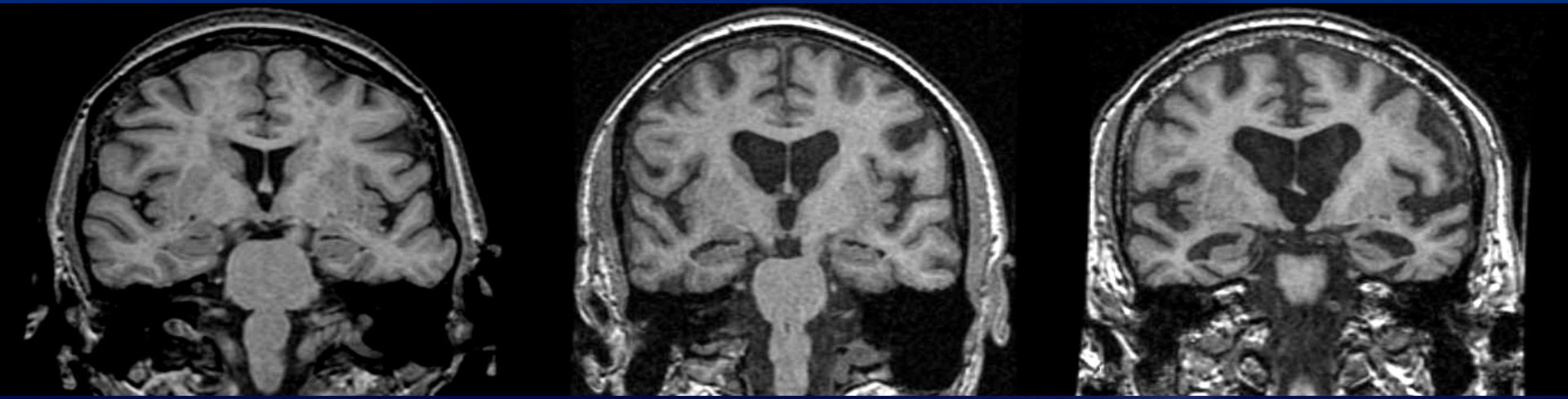
Structural MRI: Atrophy and AD Stage

Control, 70, F

MCI, 72, F

AD, 74, F



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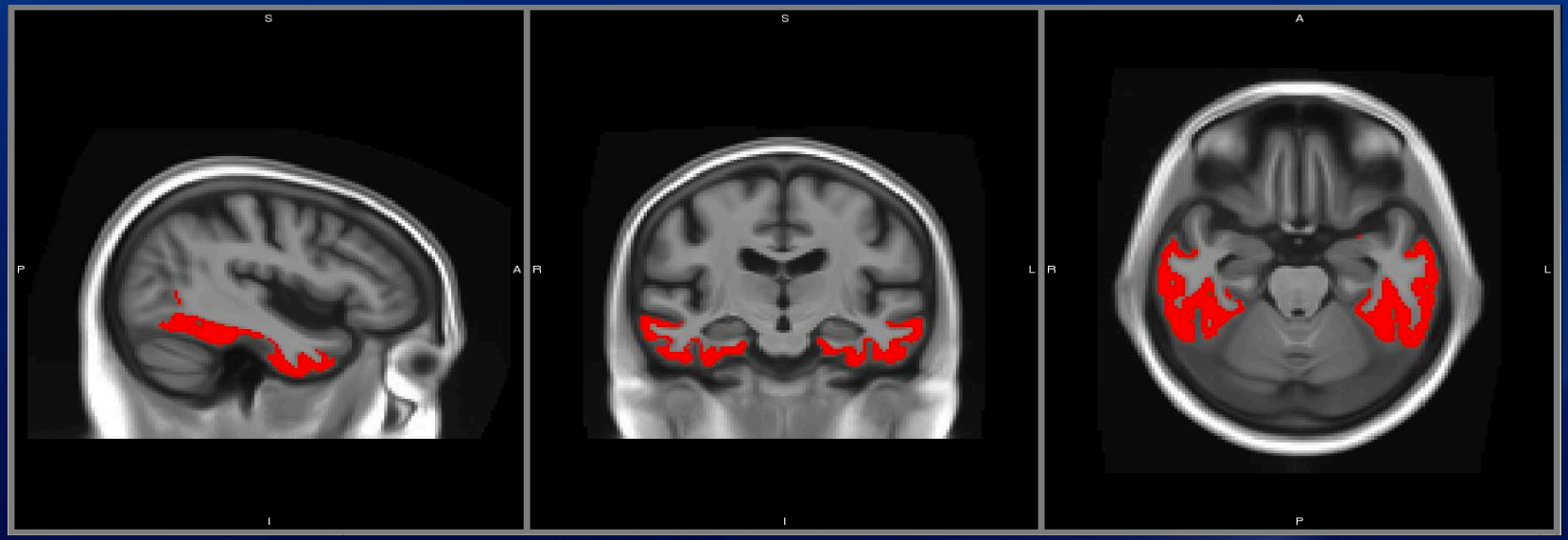
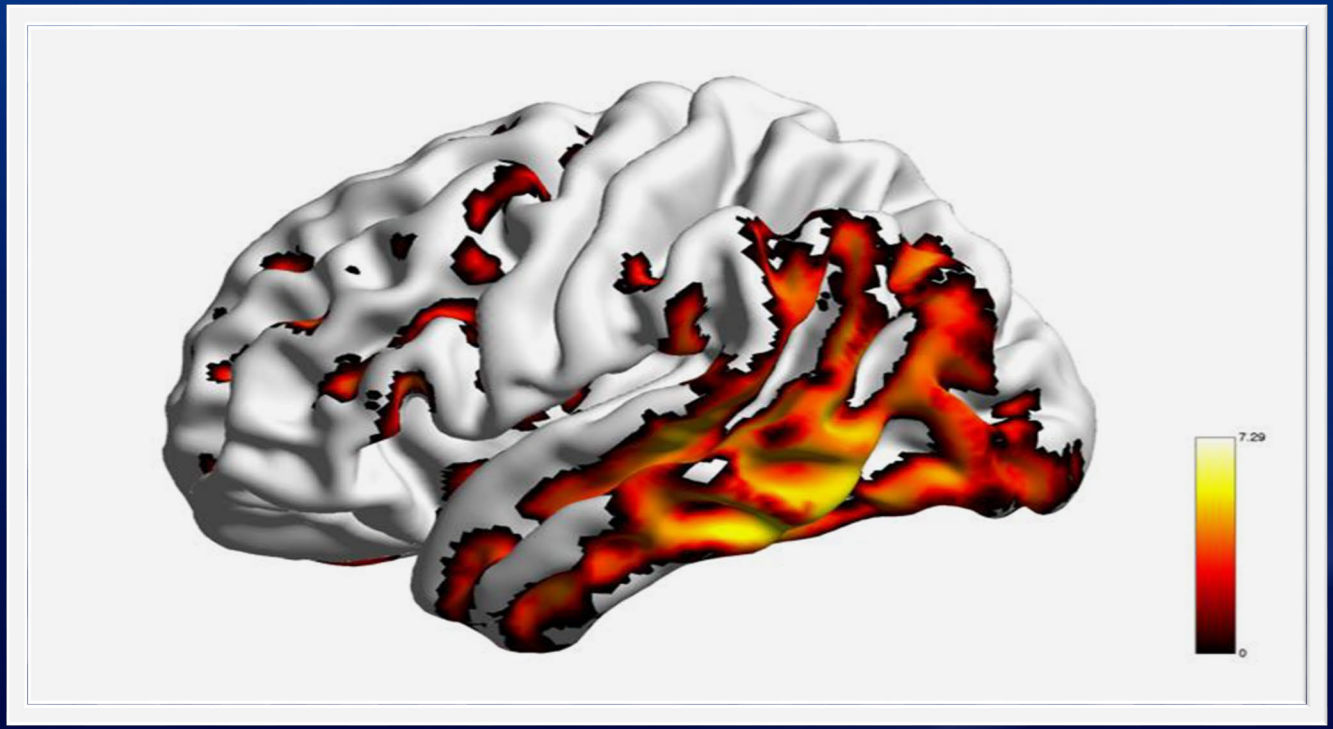
AD Signature Cortical Thickness



MRI Gray Matter Differences

Cognitively Normal vs. AD Dementia



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Functional Imaging
FDG PET

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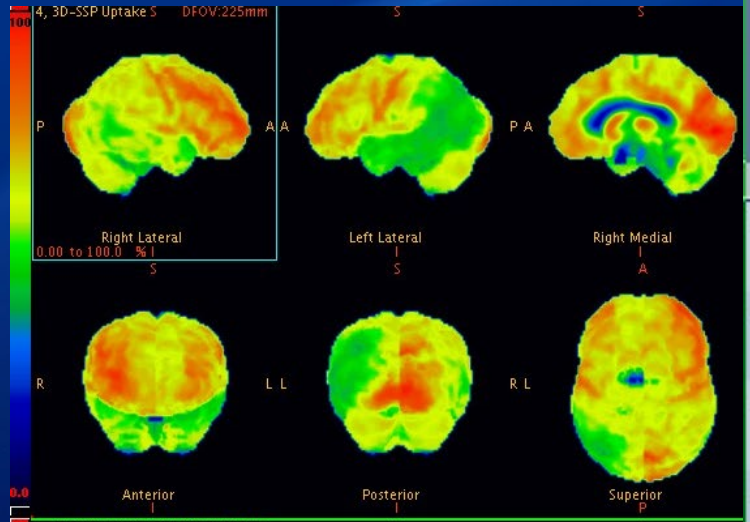

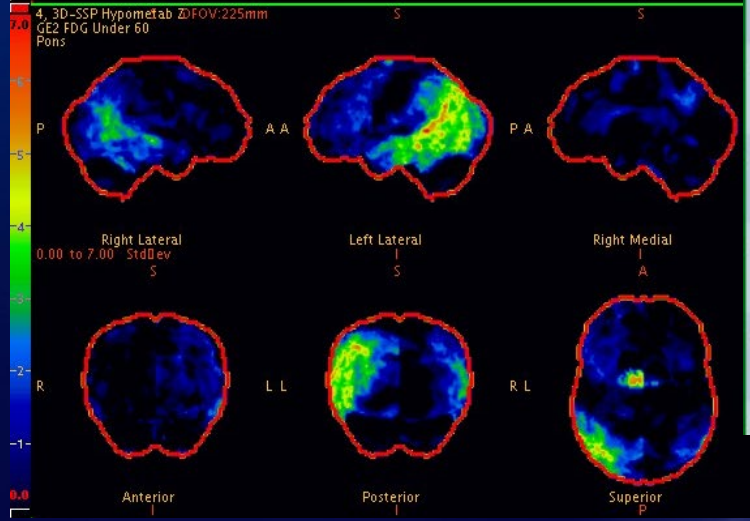

(Z-Score)

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

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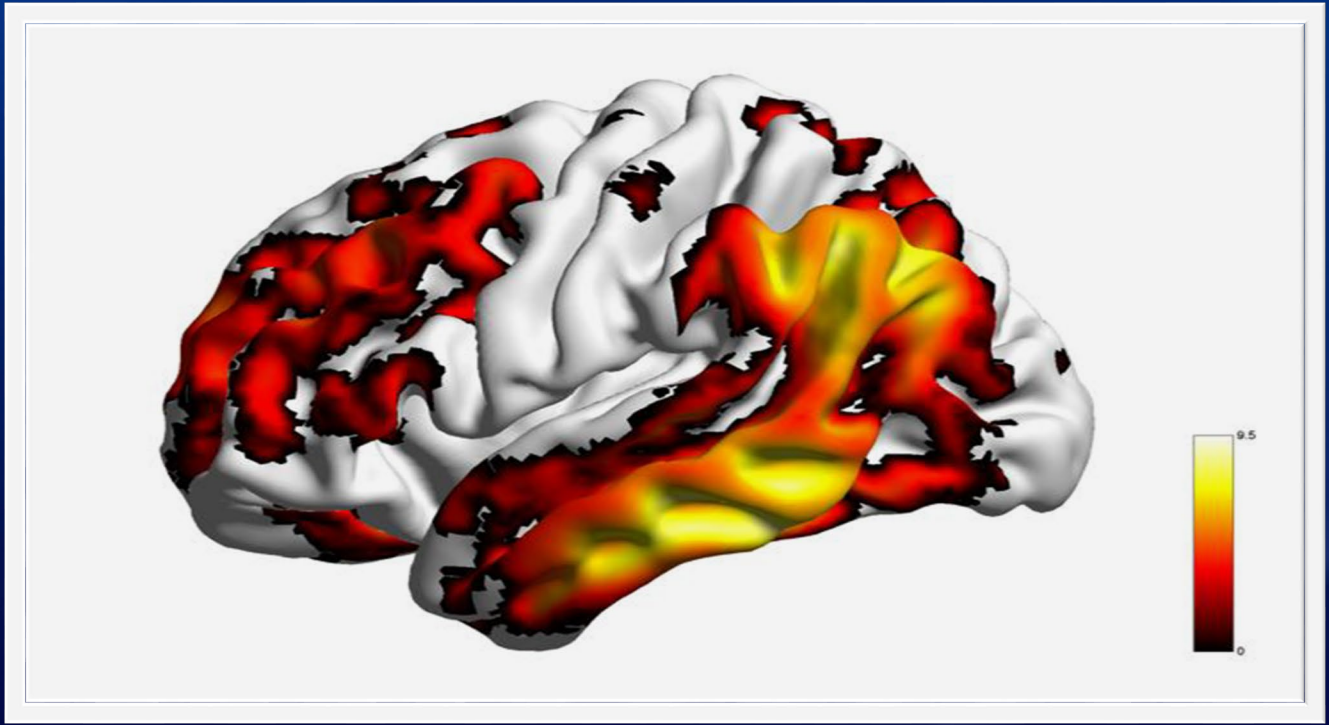
FDG PET Differences
Cognitively Normal vs. AD Dementia



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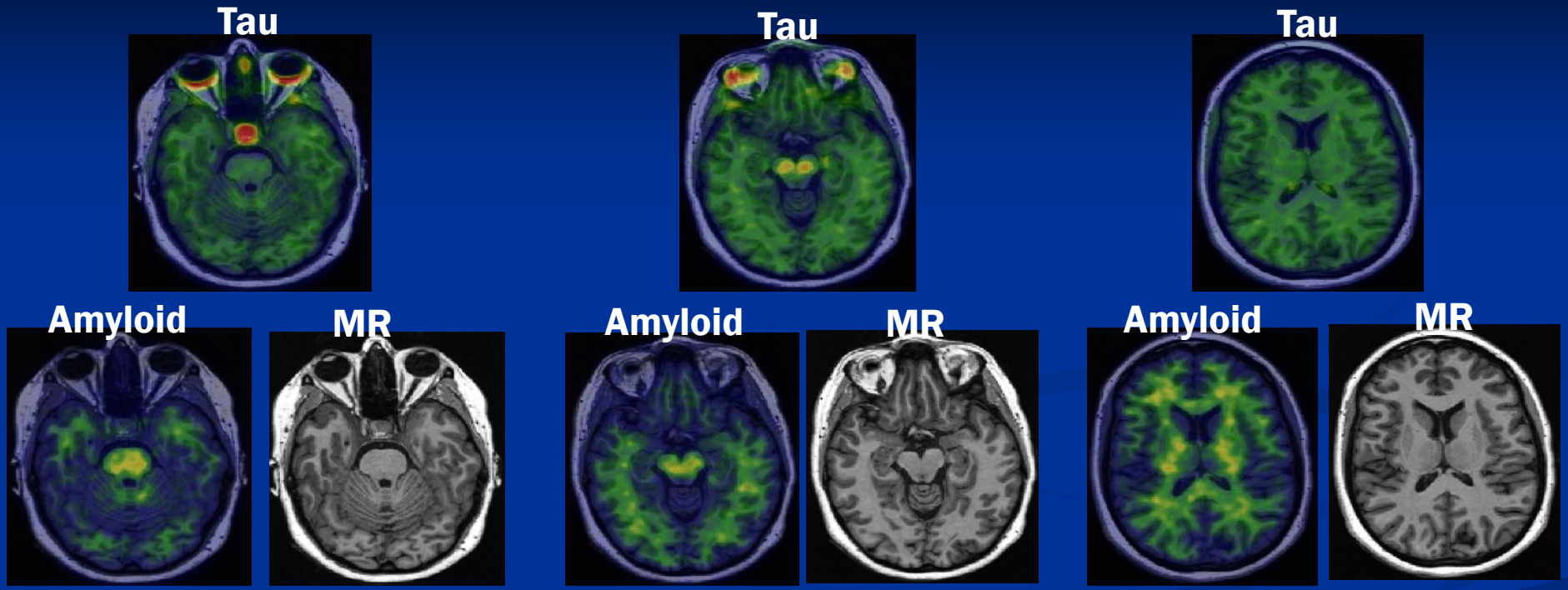
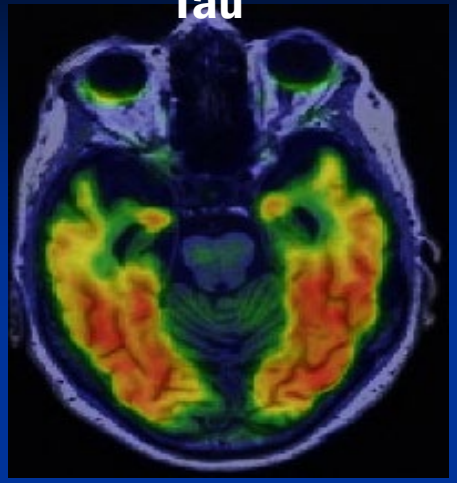
33 yo, F, cognitively unimpaired: A-T-(N)- profile

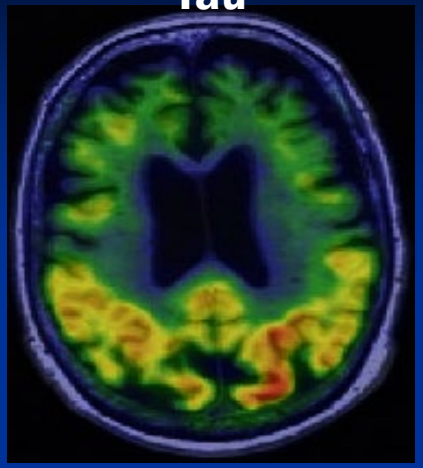


75 yo F, amnestic multi domain dementia: A+T+(N)+ profile

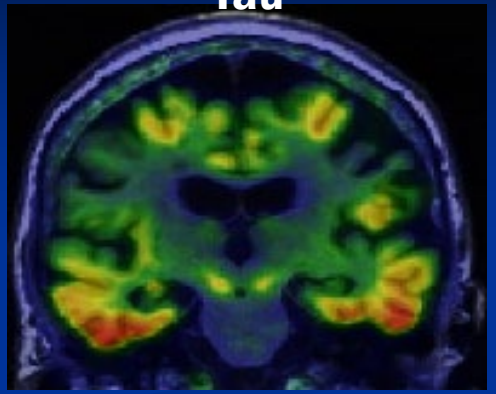
Tau



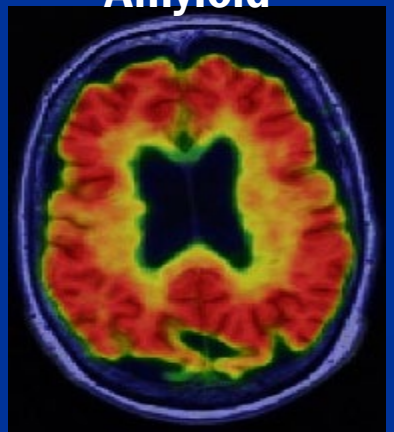
Tau



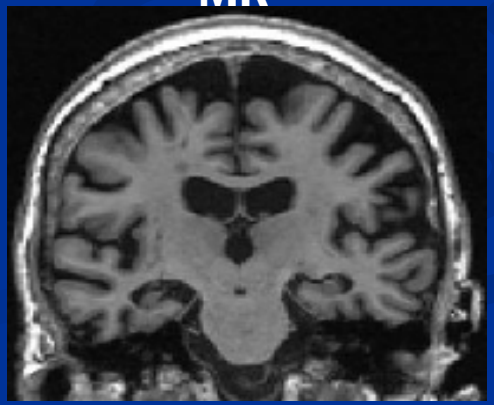
Tau



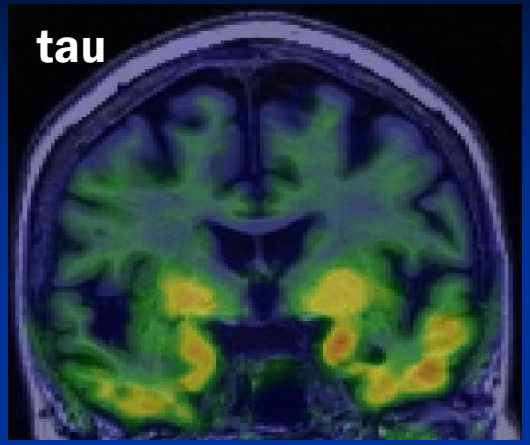
Amyloid

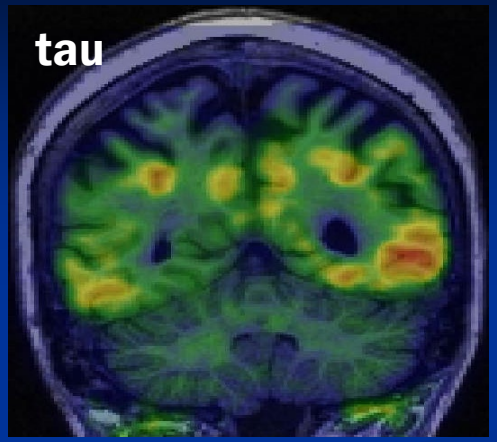


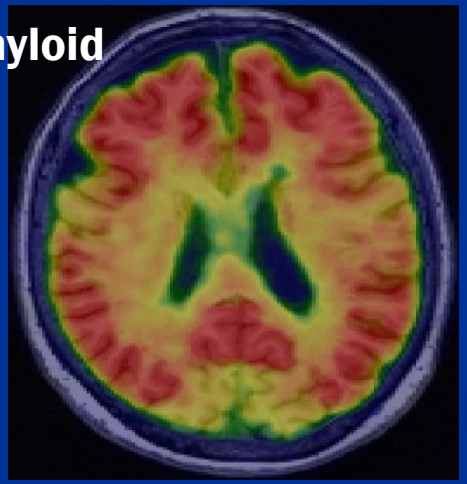
MR

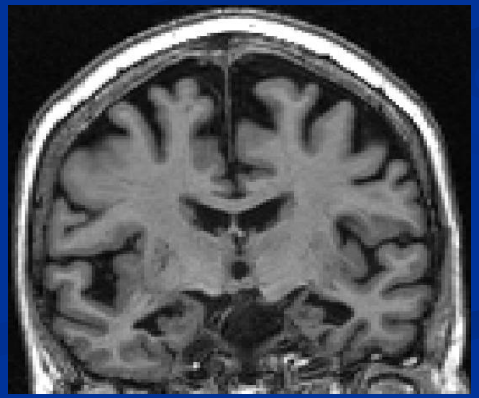


MCI A+T+N+, 88, F

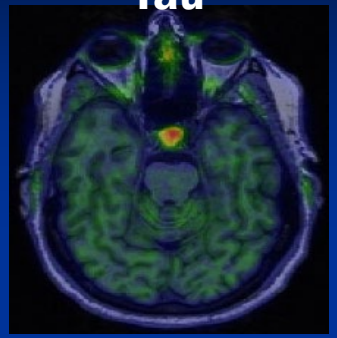


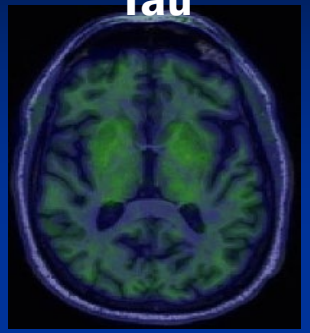


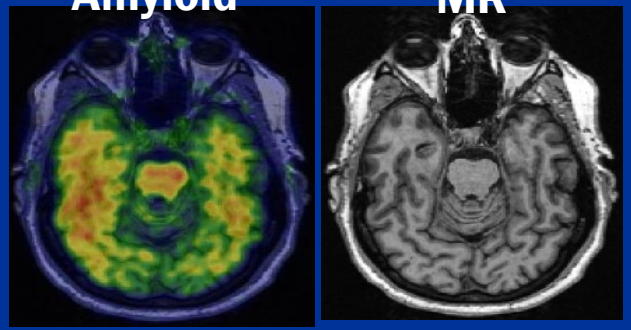


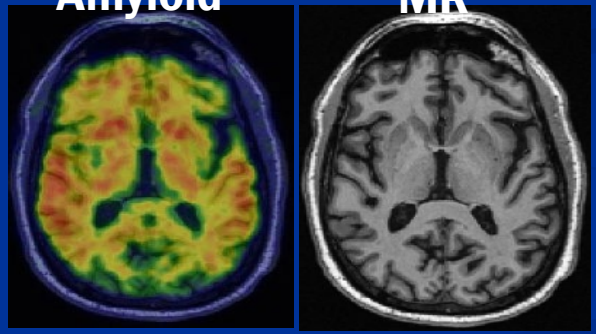


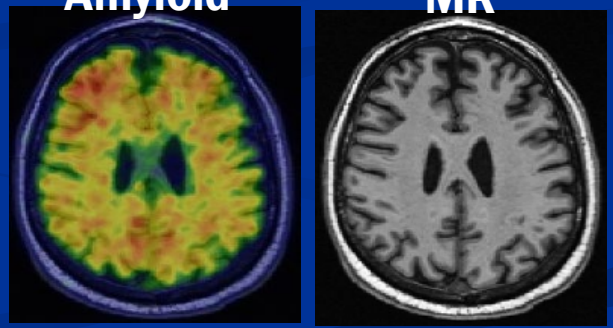
Cognitively unimpaired, 67 yo, M: A+T-(N)- profile











Amyloid pathology Tau pathology Neurodegeneration Cognitive impairment

Jack et al: Alzheimer's & Dementia 14(2018)535-562.

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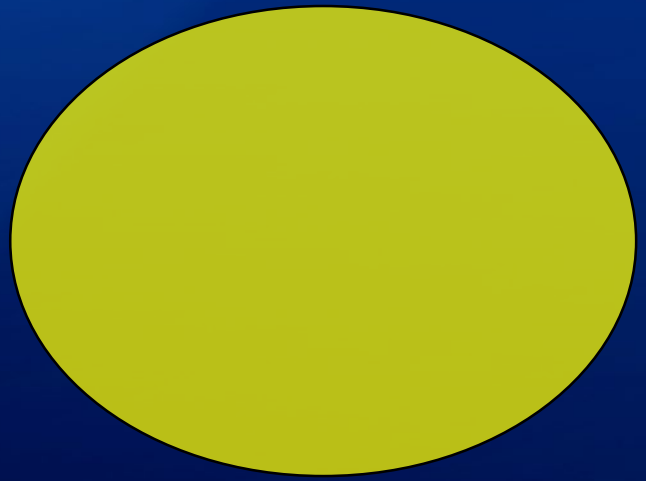
Amyloid pathology Tau pathology Neurodegeneration Cognitive impairment



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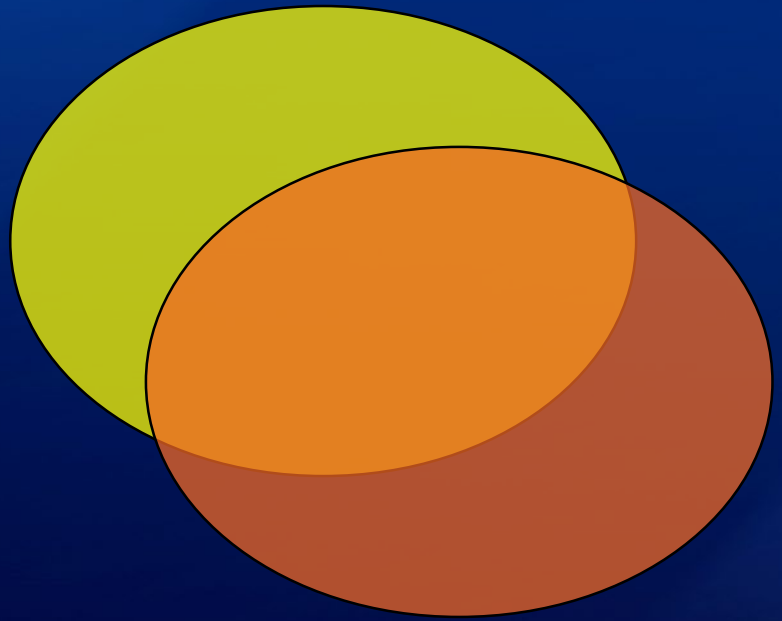

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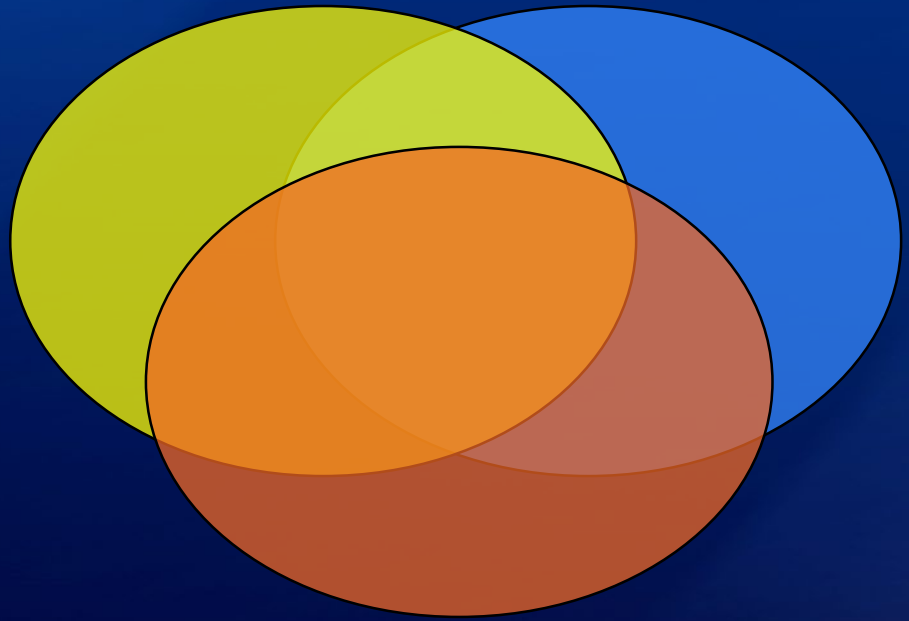

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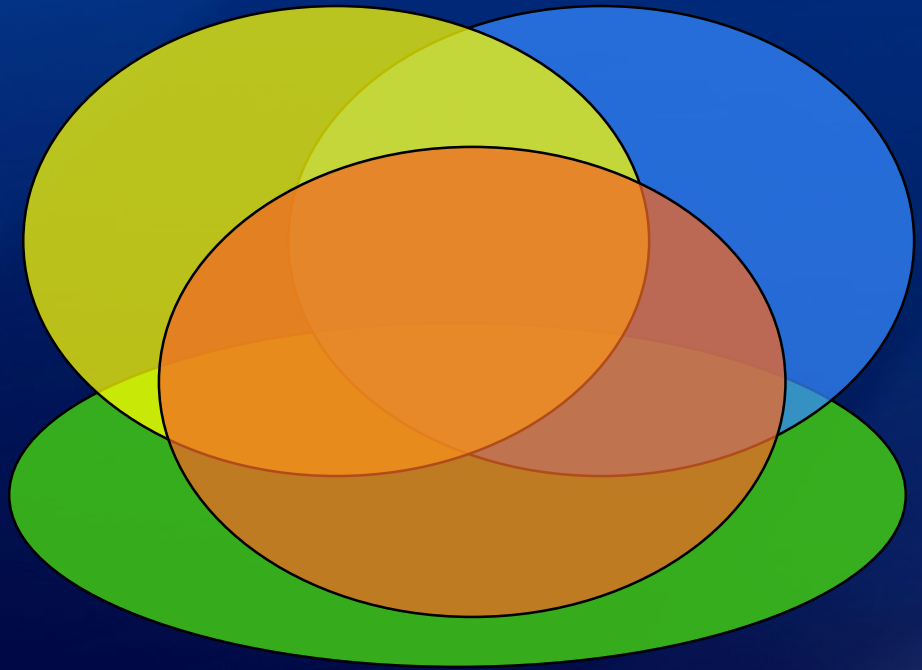

Jack et al: Alzheimer's & Dementia 14(2018)535-562.

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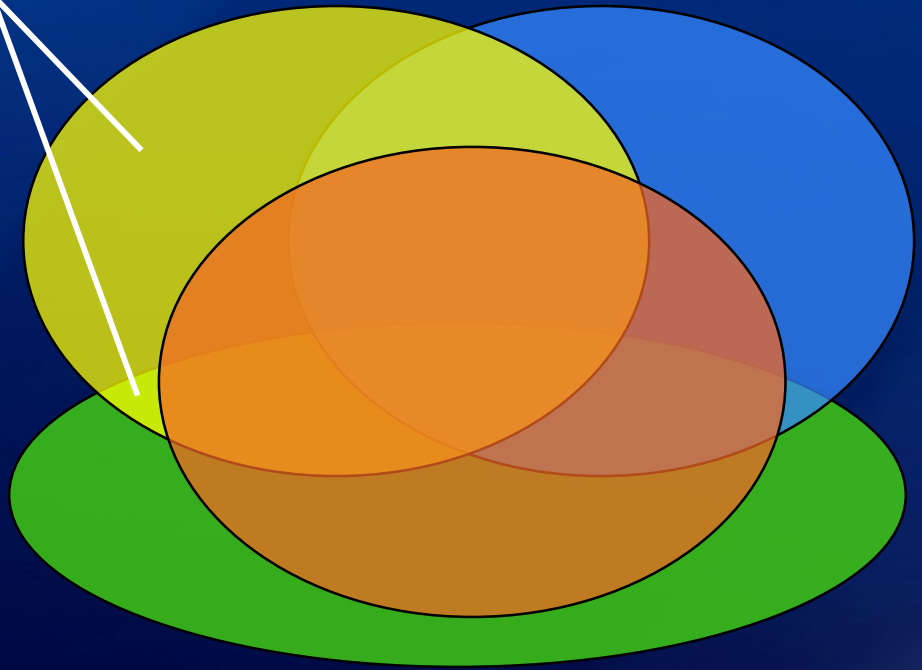
Amyloid pathology Tau pathology Neurodegeneration Cognitive impairment

Alzheimer's pathologic change



Jack et al: Alzheimer's & Dementia 14(2018)535-562.

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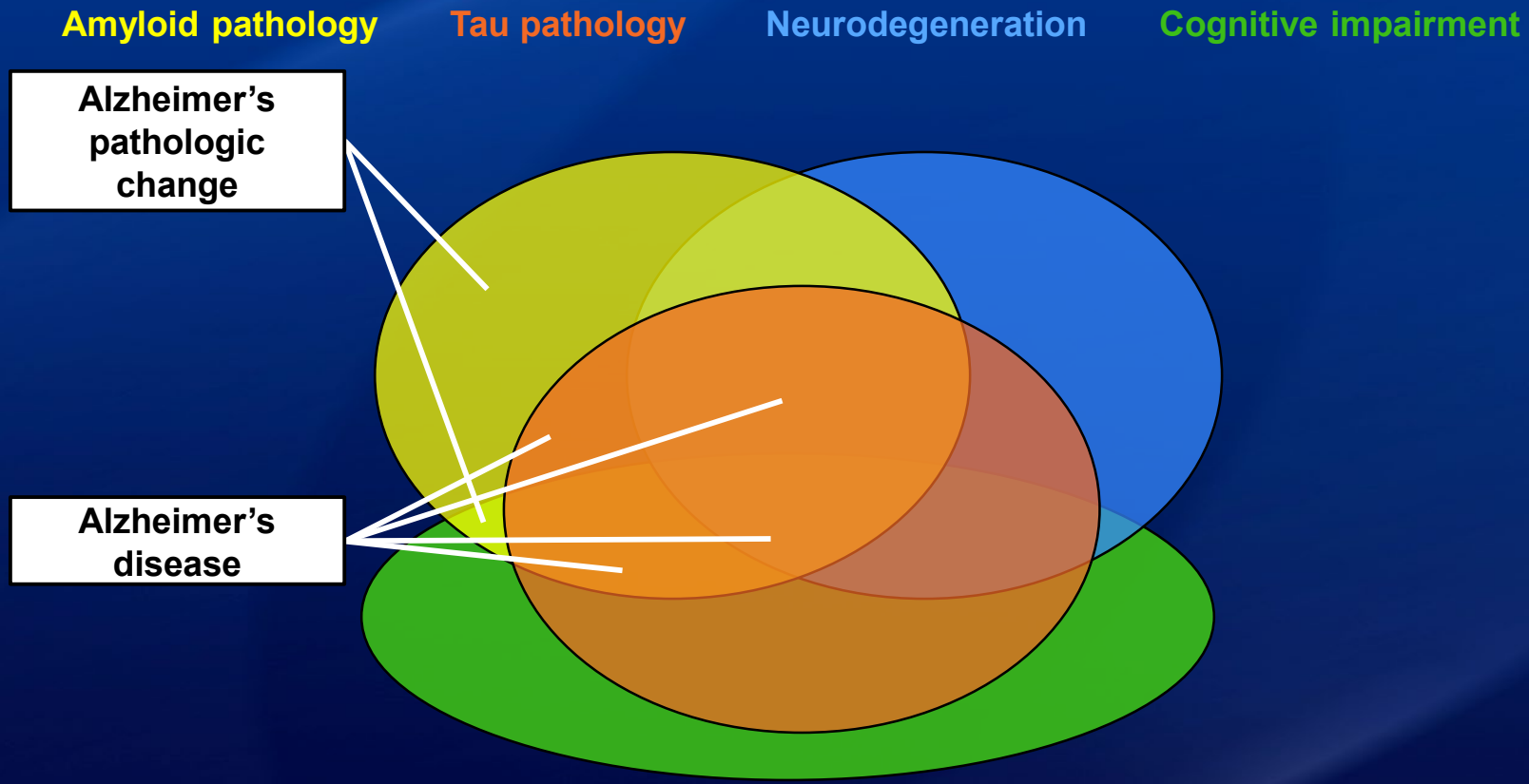

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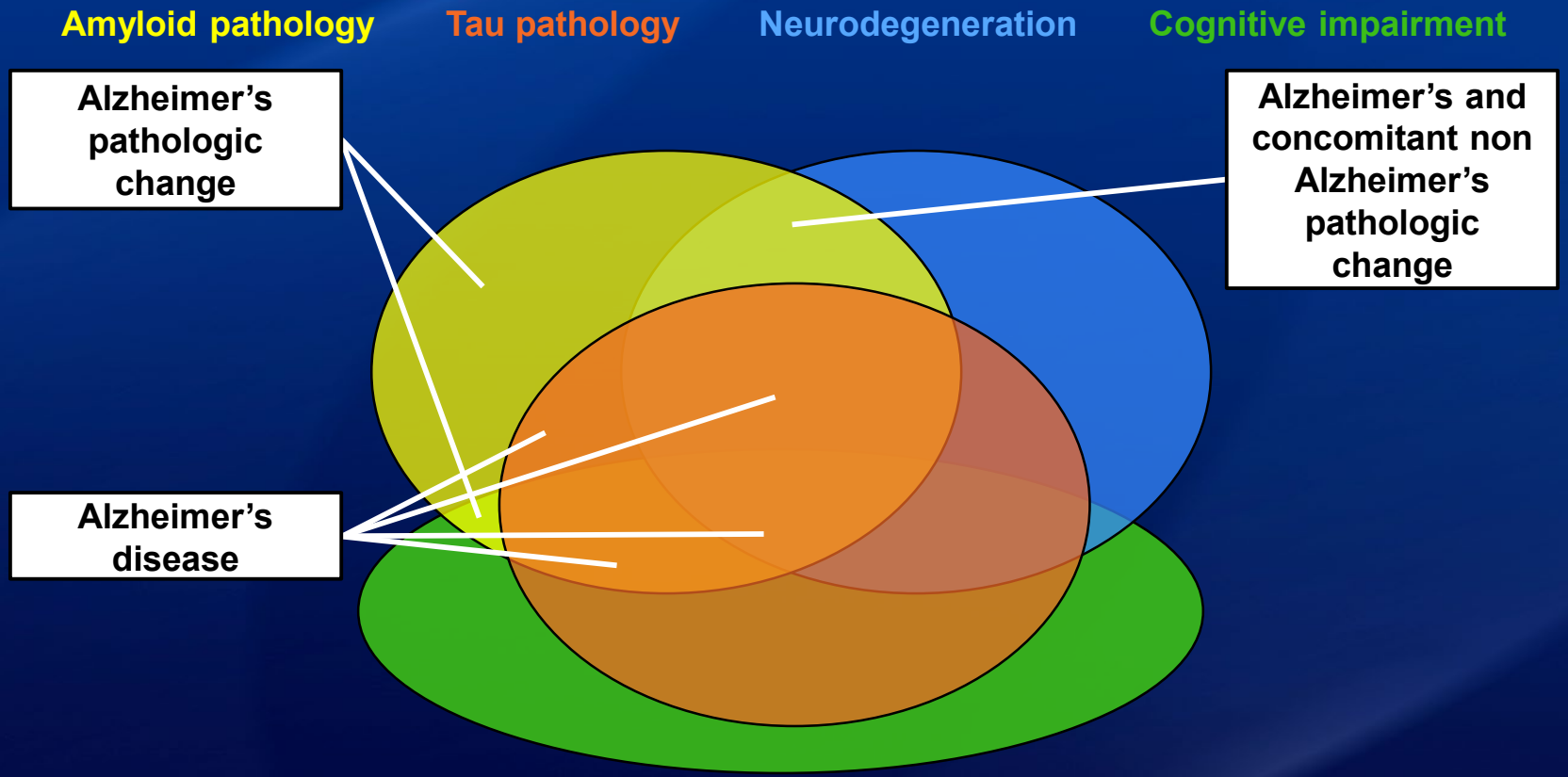

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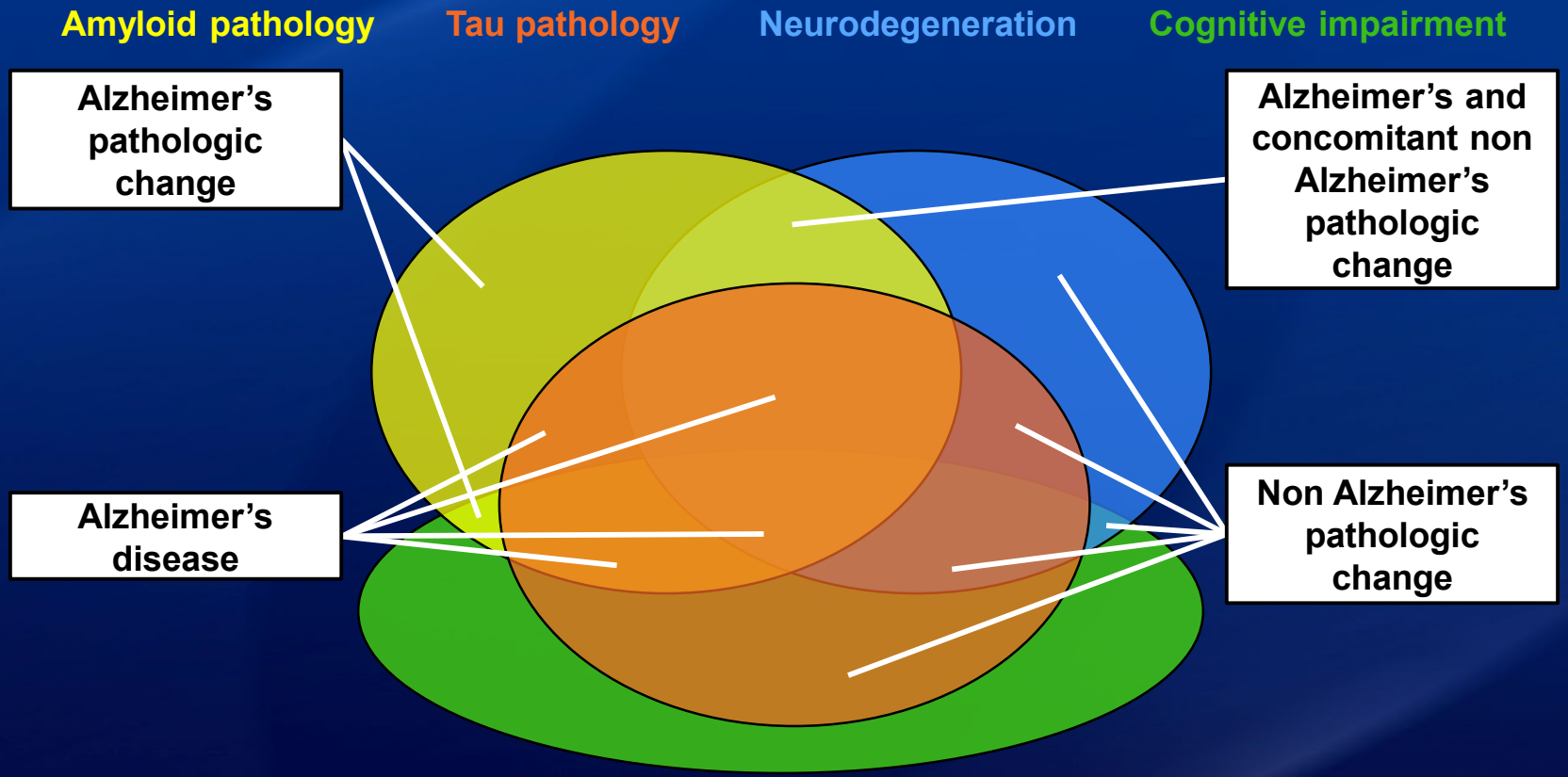

Jack et al: Alzheimer's & Dementia 14(2018)535-562.

Outline

- AD Diagnosis past and current
- ATN Framework
- **Mayo Clinic Study of Aging**
- Biomarkers in the community
- Big picture and future directions

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Mayo Clinic Study of Aging (U01 AG006786)

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Mayo Clinic Study of Aging

- Population-based study of 6900+ (3200 active) non-demented persons age 30-89 years in Olmsted County, MN

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Mayo Olmsted Study of Aging

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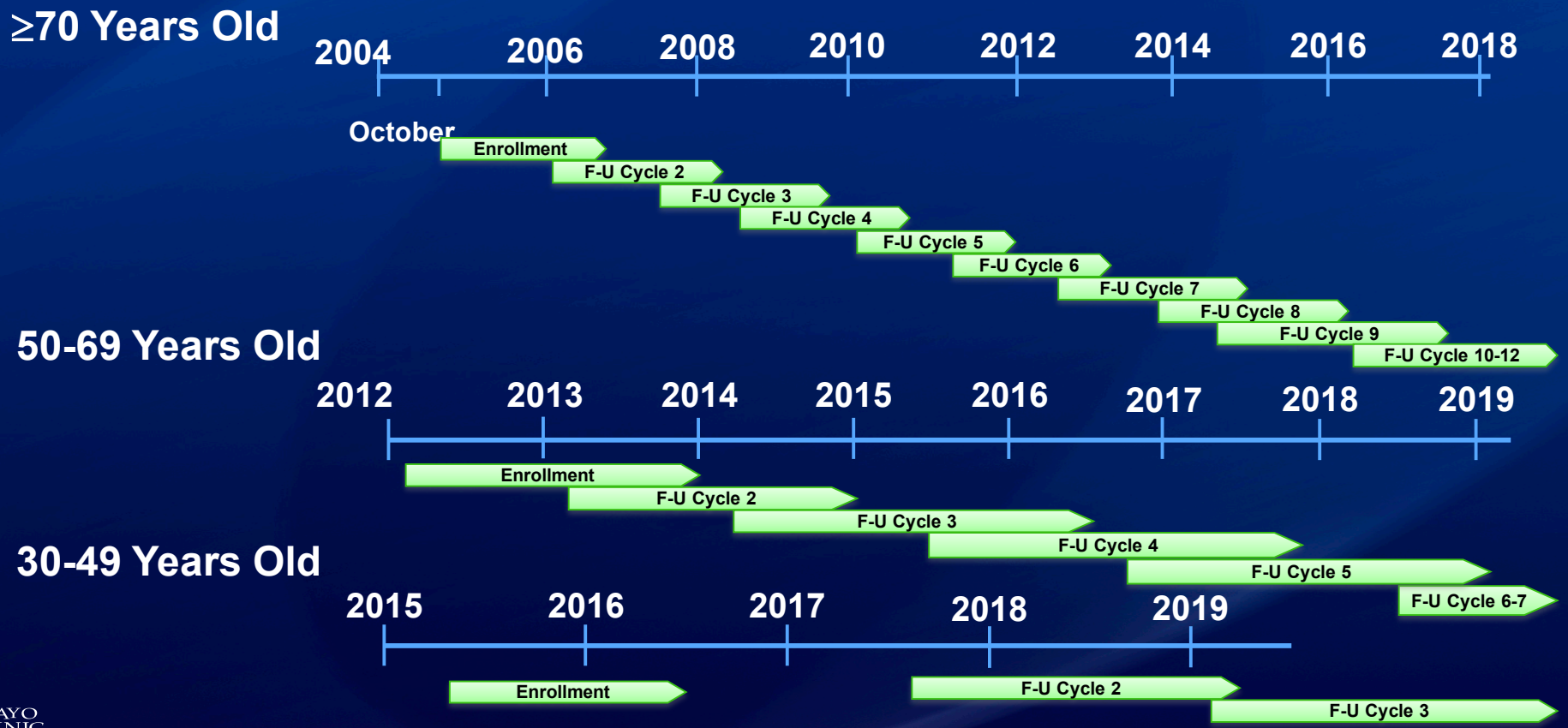
Enrollment and Follow-Up



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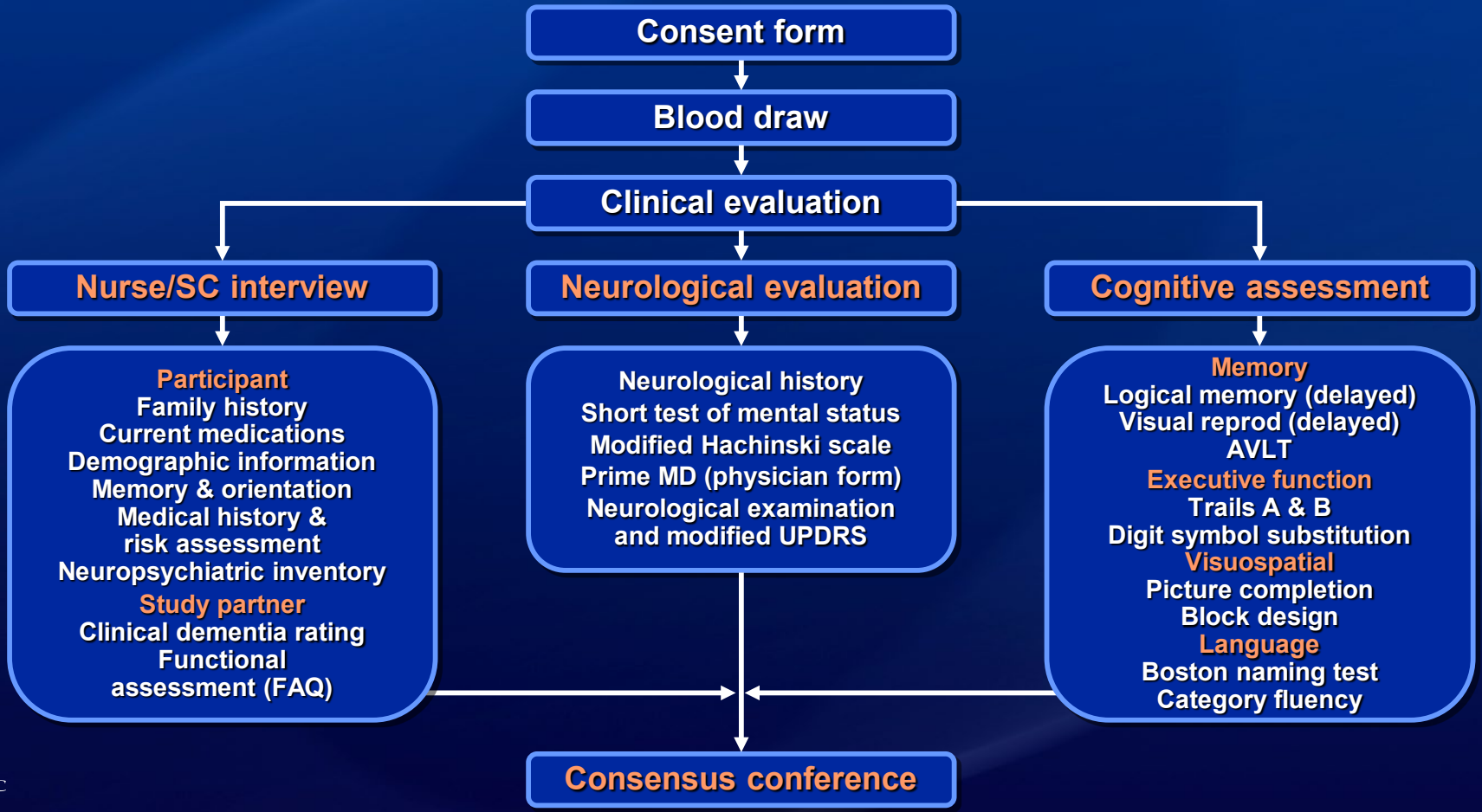
Evaluation



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Resources Acquired

- 6000+ non-demented subjects
  - 80% Cognitively normal
  - 18% MCI
  - 2% With dementia
- 6000+ quantitative MRI scans
- ~ 6000 DNA samples
- ~ 6000 frozen plasma/serum samples
  - plus annual samples
- Clinical and performance measures

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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 3300 PiB PET scans
- Performed 1200 tau PET scans

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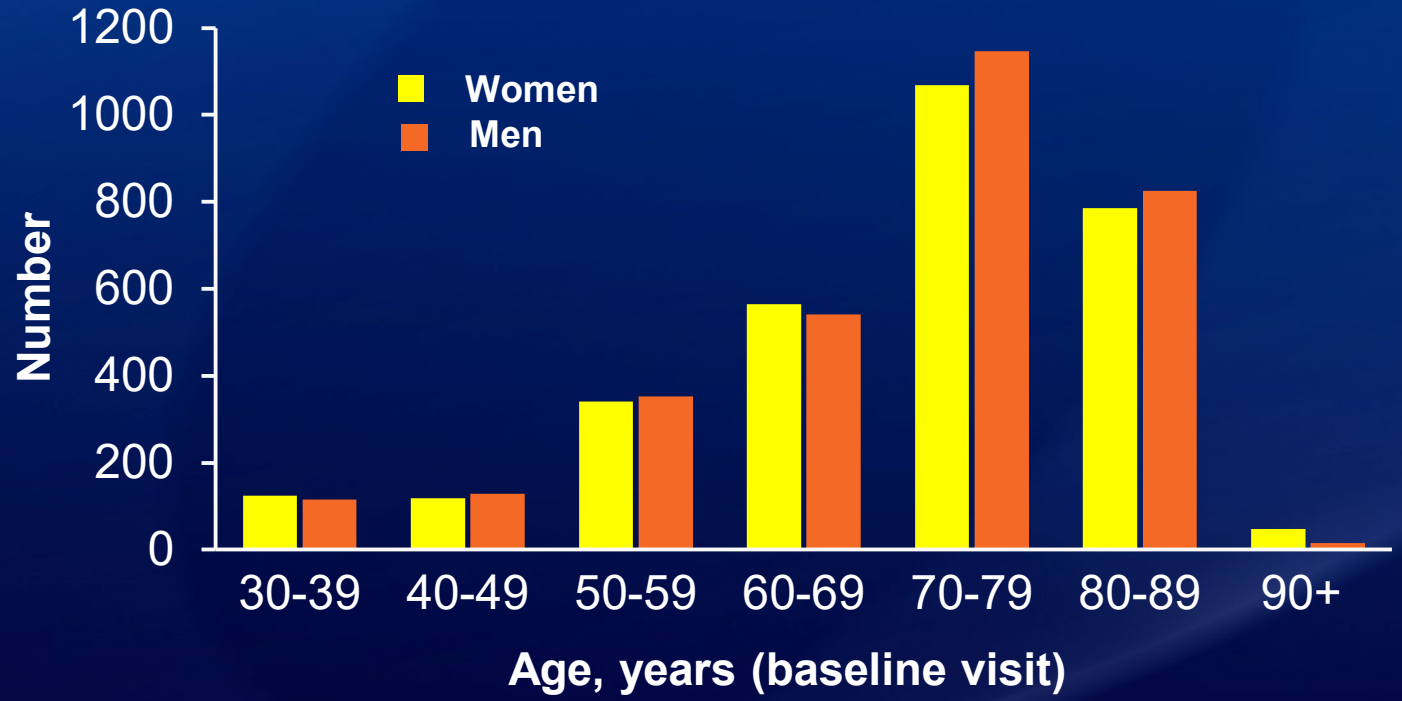
Total Participants Seen in Person by Age and Sex



Total: 6,176 (49.4% women, 50.6% men)
N: Age 30-49 = 487; 50-69 = 1,800; 70+ = 3,889

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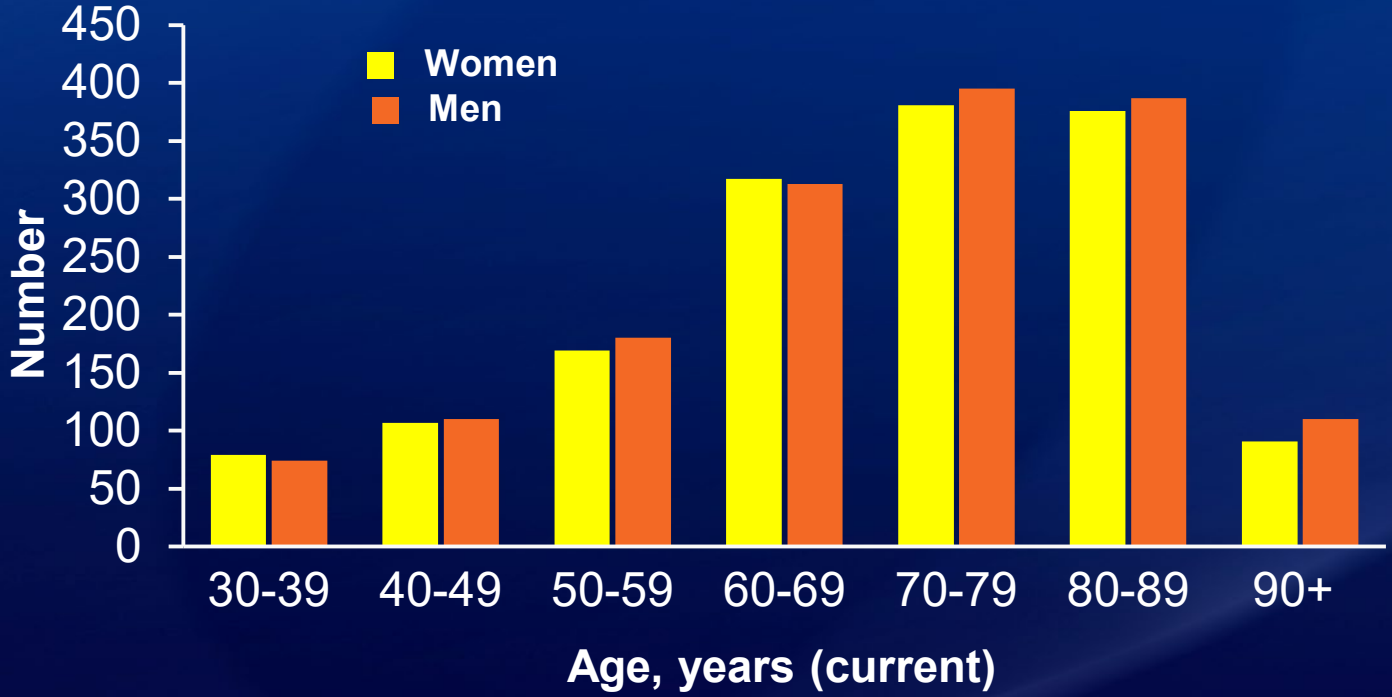
Active Participants by Age and Sex



Total: 3,089 (49.2% women, 50.8% men)
N: Age 30-49 = 370; 50-69 = 979; 70+ = 1,740

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Outline

- AD Diagnosis past and current
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Biomarkers Across the Age Spectrum

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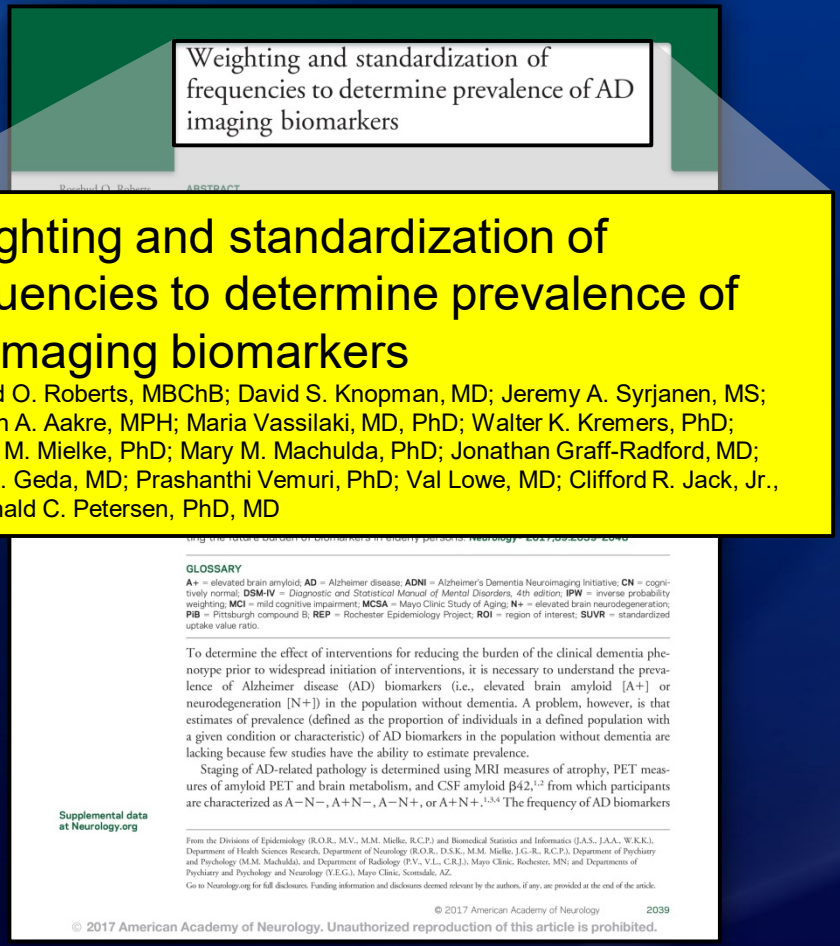


Weighting and standardization of frequencies to determine prevalence of AD imaging biomarkers

Rosebud O. Roberts, MBChB; David S. Knopman, MD; Jeremy A. Syrjanen, MS; Jeremiah A. Aakre, MPH; Maria Vassilaki, MD, PhD; Walter K. Kremers, PhD; Michelle M. Mielke, PhD; Mary M. Machulda, PhD; Jonathan Graff-Radford, MD; Yonas E. Geda, MD; Prashanthi Vemuri, PhD; Val Lowe, MD; Clifford R. Jack, Jr., MD; Ronald C. Petersen, PhD, MD

GLOSSARY

A+ = elevated brain amyloid; **AD** = Alzheimer disease; **ADNI** = Alzheimer's Dementia Neuroimaging Initiative; **CN** = cognitively normal; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; **IPW** = inverse probability weighting; **MCI** = mild cognitive impairment; **MCSA** = Mayo Clinic Study of Aging; **N+** = elevated brain neurodegeneration; **PiB** = Pittsburgh compound B; **REP** = Rochester Epidemiology Project; **ROI** = region of interest; **SUVR** = standardized uptake value ratio.

To determine the effect of interventions for reducing the burden of the clinical dementia phenotype prior to widespread initiation of interventions, it is necessary to understand the prevalence of Alzheimer disease (AD) biomarkers (i.e., elevated brain amyloid [A+] or neurodegeneration [N+]) in the population without dementia. A problem, however, is that estimates of prevalence (defined as the proportion of individuals in a defined population with a given condition or characteristic) of AD biomarkers in the population without dementia are lacking because few studies have the ability to estimate prevalence.

Staging of AD-related pathology is determined using MRI measures of atrophy, PET measures of amyloid PET and brain metabolism, and CSF amyloid β42,[1,2] from which participants are characterized as A−N−, A+N−, A−N+, or A+N+.[1,3,4] The frequency of AD biomarkers

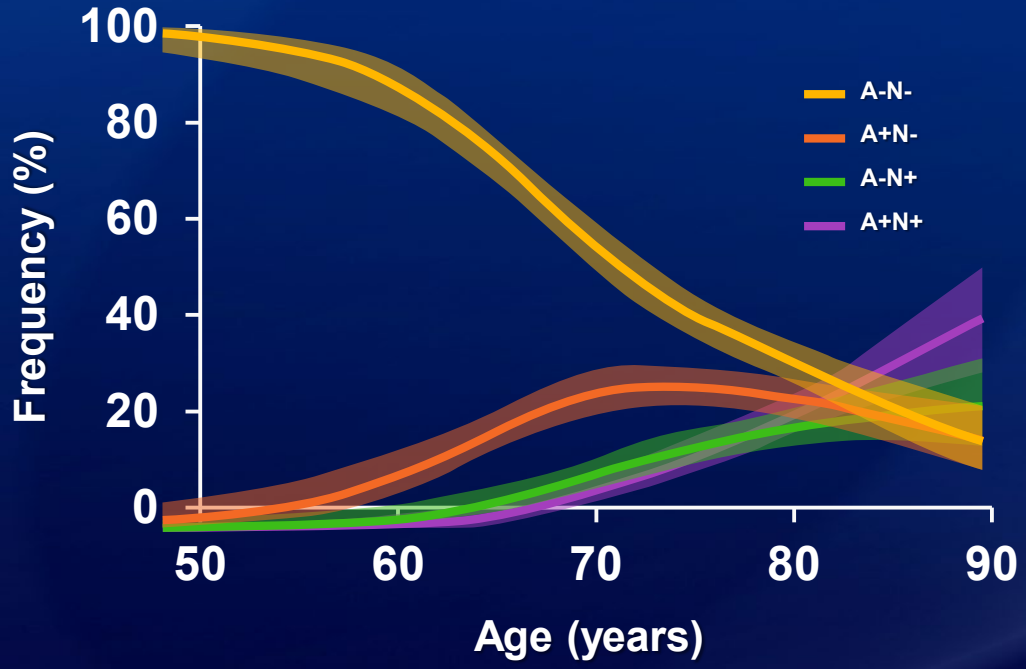
Supplemental data at Neurology.org

From the Divisions of Epidemiology (R.O.R., M.V., M.M. Mielke, R.C.P.) and Biomedical Statistics and Informatics (J.A.S., J.A.A., W.K.K.), Department of Health Sciences Research, Department of Neurology (R.O.R., D.S.K., M.M. Mielke, J.G.-R., R.C.P.), Department of Psychiatry and Psychology (M.M. Machulda), and Department of Radiology (P.V., V.L., C.R.J.), Mayo Clinic, Rochester, MN; and Departments of Psychiatry and Psychology and Neurology (Y.E.G.), Mayo Clinic, Scottsdale, AZ.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Neurology® 2017;89:2039-2048

Population Frequencies of Biomarkers in Typical AD



Jack et al: Lancet Neurol 13:997, 2014

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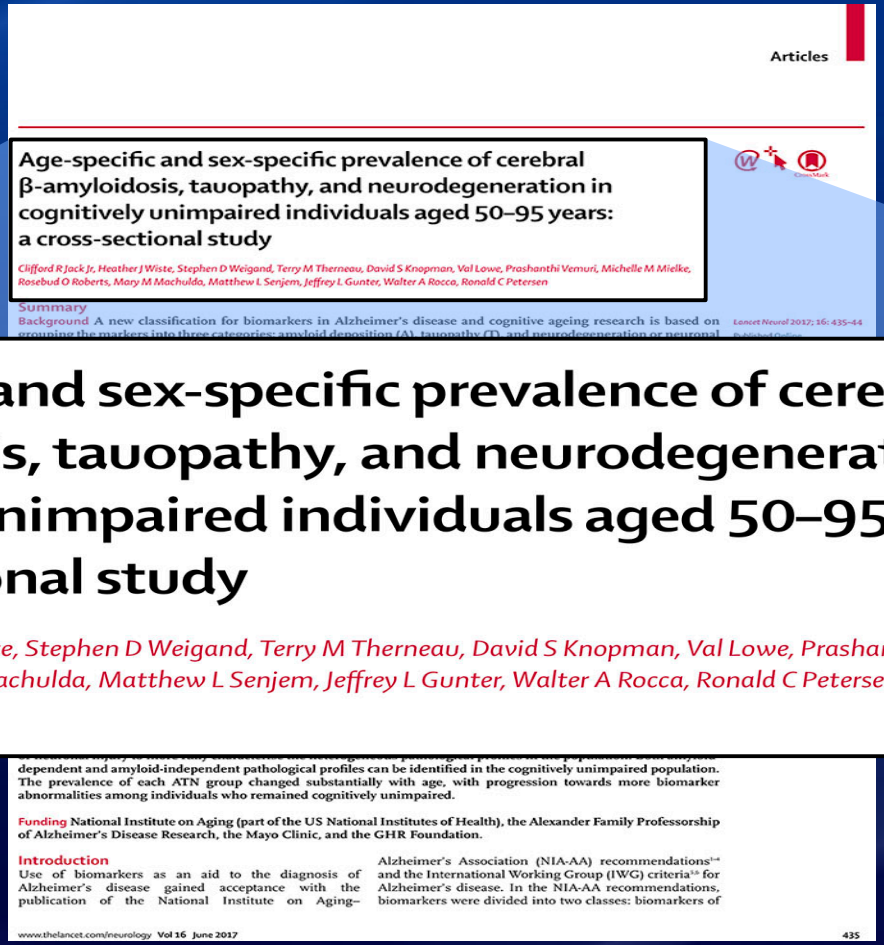

Articles

Age-specific and sex-specific prevalence of cerebral β-amyloidosis, tauopathy, and neurodegeneration in cognitively unimpaired individuals aged 50–95 years: a cross-sectional study

Clifford R Jack Jr, Heather J Wiste, Stephen D Weigand, Terry M Therneau, David S Knopman, Val Lowe, Prashanthi Vemuri, Michelle M Mielke, Rosebud O Roberts, Mary M Machulda, Matthew L Senjem, Jeffrey L Gunter, Walter A Rocca, Ronald C Petersen

Summary

Background A new classification for biomarkers in Alzheimer's disease and cognitive ageing research is based on

Lancet Neurol 2017; 16: 435–44

Age-specific and sex-specific prevalence of cerebral β-amyloidosis, tauopathy, and neurodegeneration in cognitively unimpaired individuals aged 50–95 years: a cross-sectional study

Clifford R Jack Jr, Heather J Wiste, Stephen D Weigand, Terry M Therneau, David S Knopman, Val Lowe, Prashanthi Vemuri, Michelle M Mielke, Rosebud O Roberts, Mary M Machulda, Matthew L Senjem, Jeffrey L Gunter, Walter A Rocca, Ronald C Petersen

Lancet Neurol 2017; 16: 435–44

dependent and amyloid-independent pathological profiles can be identified in the cognitively unimpaired population. The prevalence of each ATN group changed substantially with age, with progression towards more biomarker abnormalities among individuals who remained cognitively unimpaired.

Funding National Institute on Aging (part of the US National Institutes of Health), the Alexander Family Professorship of Alzheimer's Disease Research, the Mayo Clinic, and the GHR Foundation.

Introduction

Use of biomarkers as an aid to the diagnosis of Alzheimer's disease gained acceptance with the publication of the National Institute on Aging–Alzheimer's Association (NIA-AA) recommendations[1–4] and the International Working Group (IWG) criteria[5,6] for Alzheimer's disease. In the NIA-AA recommendations, biomarkers were divided into two classes: biomarkers of

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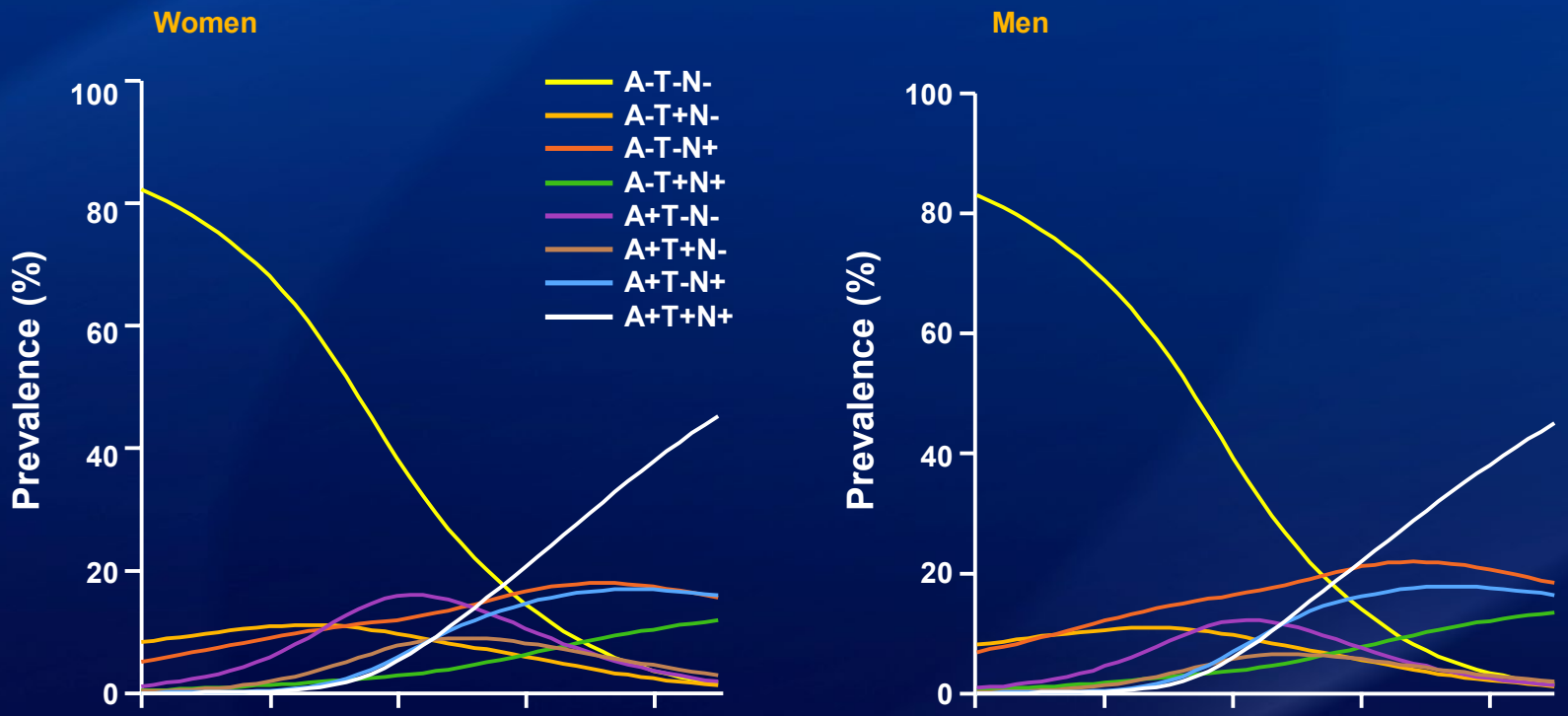
Prevalence of ATN Biomarkers Groups



Jack et al. Lancet Neurology June 2017;16:435-444

JAMA Neurology | Original Investigation

Prevalence of Biologically vs Clinically Defined Alzheimer Spectrum Entities Using the National Institute on Aging–Alzheimer's Association Research Framework

July 2019

Clifford R. Jack Jr, MD; Terry M. Therneau, PhD; Stephen D. Weigand, MS; Heather J. Wiste, BA; David S. Knopman, MD; Prashanthi Vemuri, PhD; Val J. Lowe, MD; Michelle M. Mielke, PhD; Rosebud O. Roberts, MB, ChB; Mary M. Machulda, PhD; Jonathan Graff-Radford, MD; David T. Jones, MD; Christopher G. Schwarz, PhD; Jeffrey L. Gunter, PhD; Matthew L. Senjem, MS; Walter A. Rocca, MD; Ronald C. Petersen, MD, PhD

Objective

- What are the age- and sex-specific prevalences of the three biological markers in the AD research framework in various combinations compared to the clinical syndromic conditions associated with AD?

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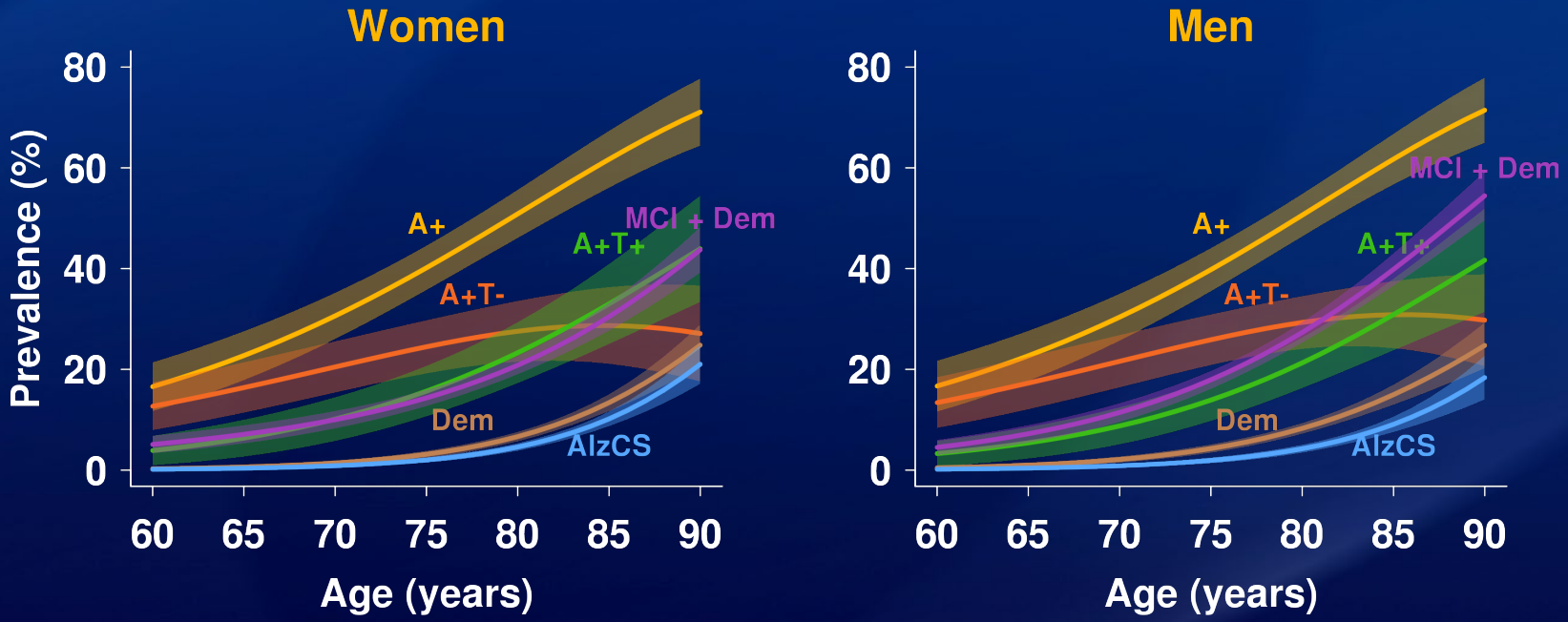
Prevalence of Biologically vs Clinically Defined Alzheimer Disease



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Prevalence of Biological and Clinical AD

- Prevalence of A+T+ exceeds clinical AD at any age
- At age 85, the prevalence of biological AD is 3X clinical dementia due to AD
- Most of the differences are due to asymptomatic AD
- Utility: planning of clinical trials

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Outline

- AD Diagnosis past and current
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- Biomarkers in the community
- **Big picture and future directions**

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But, at the end of the day…

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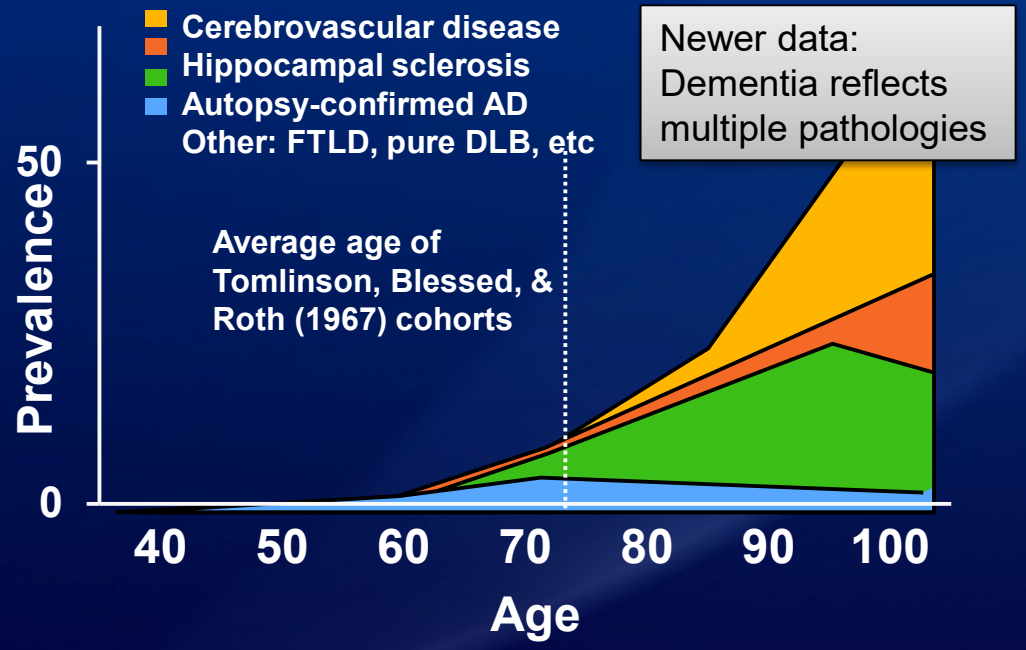
Many Pathologies Increase in Prevalence With Age in Addition to AD

- Cerebrovascular disease
- PART
- Lewy body disease
- Hippocampal sclerosis
- TDP 43
- Argyrophillic grains
- Mixed path most common



Nelson: Acta Neuropath, 2011

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Three Broad Mechanisms of CVD

- Small vessel disease related to hypertensive arteriopathy or SVD-H
- Small vessel disease related to cerebral amyloid angiopathy or SVD-CAA
- Large (embolic/occlusive) vessel disease or LVD

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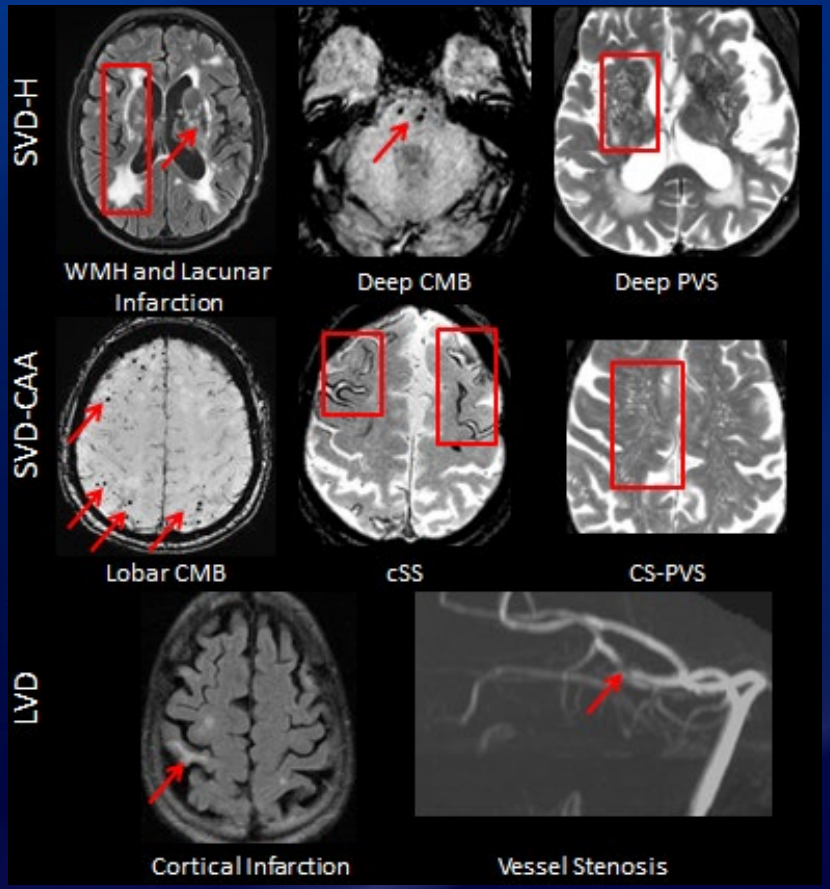
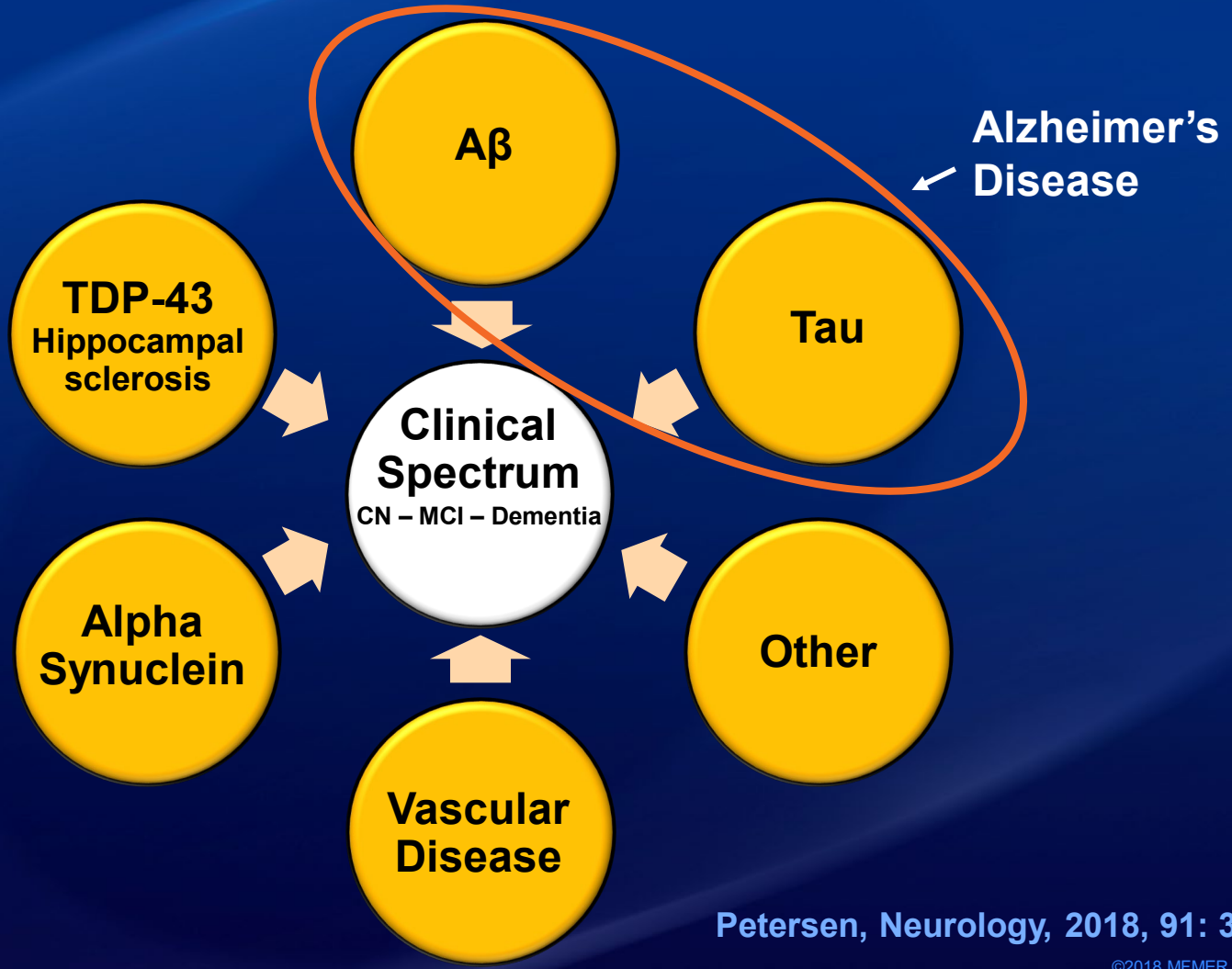
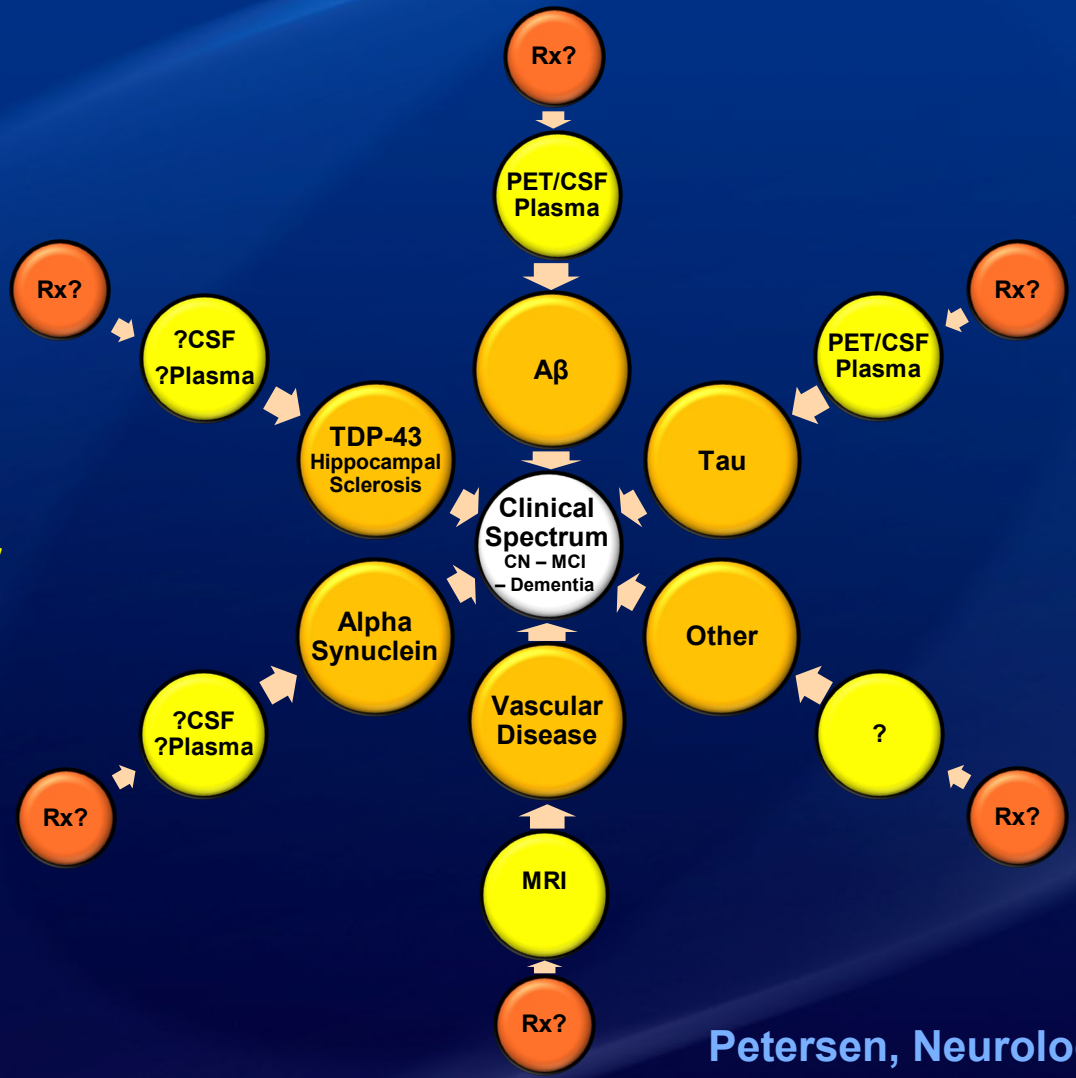
Measurements using MRI





Petersen, Neurology, 2018, 91: 395-402

Clinical
Pathology
Biomarker
Therapy



Petersen, Neurology, 2018, 91: 395-402

Summary: Biomarkers and AD

- NIA-AA Research Framework feasible
- Role of biomarkers increasingly important
- Clinical diagnosis remains vital
- But, multiple co-pathologies common
- Work to do

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Mayo Clinic Mayo Aging Research

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Jon Graff-Radford
Dave Jones
Prashanthi Vemuri
Walter Rocca
Terry Therneau
Walter Kremers
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Len Petrucelli
Guojun Bu
Owen Ross

Scottsdale

Rick Caselli
Bryan Woodruff

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Thank You

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