Changing Definitions of Alzheimer's Disease and the Role of Biomarkers

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ASC BrainXchange Webinar

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Learning Objectives

- Understanding how diagnostic criteria for AD have evolved in response to growing understanding of the disease and advances in technology
- Understanding the role of biomarkers in AD
  - What are the biomarkers of AD?
  - How can they add value?
  - Which ones are available now? In the future?

Diagnostic Criteria for AD

- 1906: Dr. Alois A. describes first case of AD
  - Dx, thereafter, based on autopsy (plaques & tangles)
- 1984: First diagnostic criteria: NINCDS-ADRDA "McKhann" criteria
  - Dx based on clinical criteria (medical hx, exam, and ruling out other conditions)
  - Some Assumptions:
    - AD=AD dementia; age limits is 40-90 years of age; memory loss is the most prominent feature

First Formal Diagnostic Criteria for AD: NINCDS-ADRDA 1984 criteria

- Categories: Probable, possible, autopsy confirmed
- Probable AD: based on what was felt at the time to be the phenotype of AD (progressive memory deficit, insidious onset,, impact on daily function, not caused by X,Y,Z.
- Probable AD dx thought at best 85% accurate in expert hands
- Used in clinical dx & for inclusion in AD clinical trials, including the pivotal trials for CHEIs and memantine

2011: Revised Diagnostic Criteria for AD NIA-AA 2011

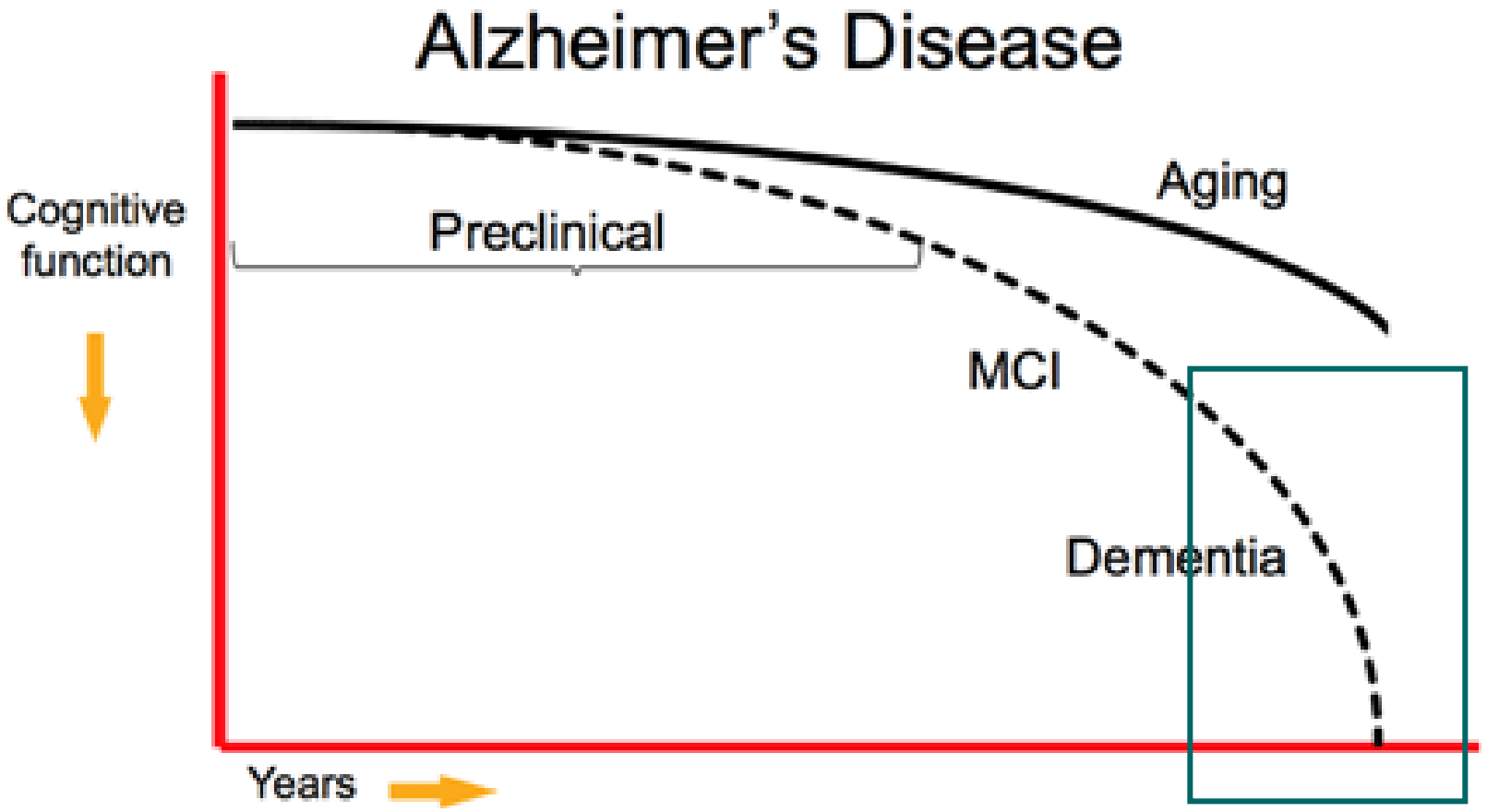
- Reflected more advanced understanding of:
  - sequence of brain changes in AD
  - non-amnestic variants of AD (PPA, PCA, dysexecutive)
  - age range affected by AD
  - gene mutations as a rare direct cause of AD
  - other diseases mimicking AD which were not yet known in 1984 (e.g., FTD; DLB; CBD)

2011 Criteria Reflected New Concepts in AD Pathophysiology

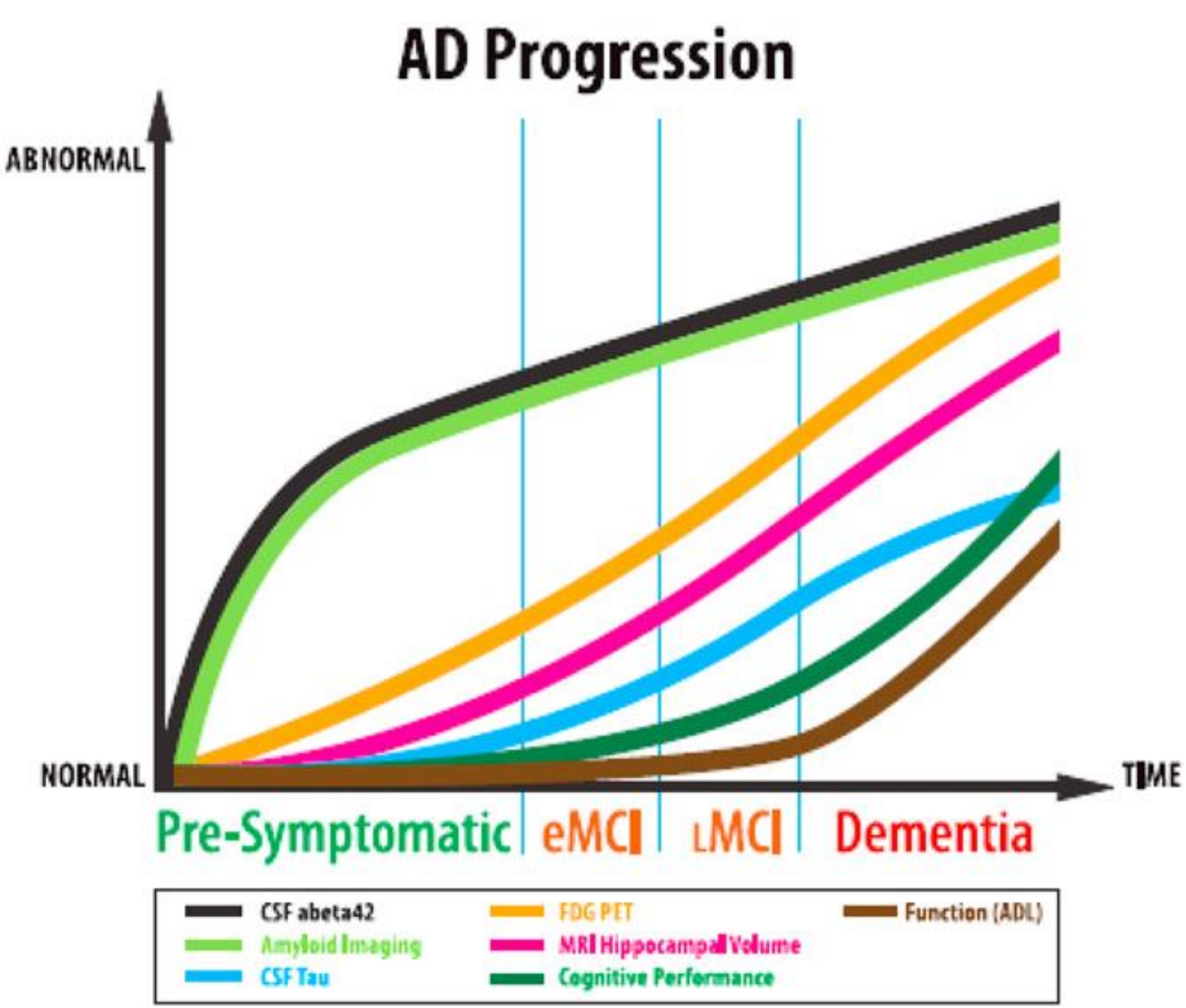
- AD is a longer disease than previously reported
- Brain changes predate symptoms by ≥ 20 years
- The initial stage of AD is clinically silent
- The earliest symptomatic stage ("MCI due to AD") can last 5 or more years
- Dementia is the *end stage* of AD
- Biomarker can increase diagnostic certainty

NIA-AA 2011 Diagnostic Criteria

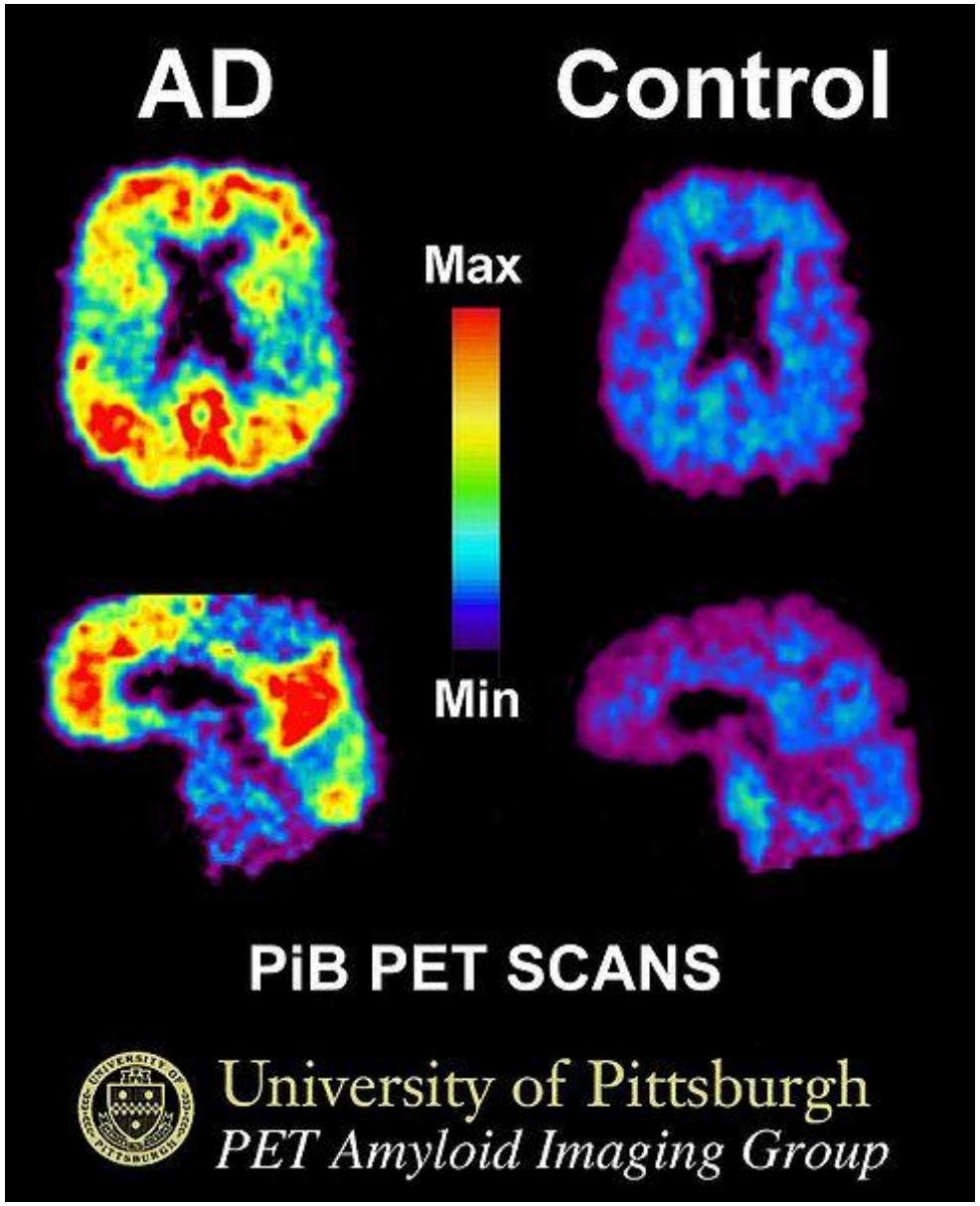
- 3 stages of AD recognized:
  - Preclinical AD, MCI due to AD, AD Dementia
- 5 biomarkers recognized:
  - 3 imaging biomarkers (MRI MTL, glu PET, amyloid PET)
  - 2 CSF biomarkers (amyloid and tau levels)
- biomarkers used to ***rule in*** AD not simply rule out other diseases



A 30 yr disease: 15 + 5 + 10


AD Progression
ABNORMAL
NORMAL
TIME
Pre-Symptomatic
eMCI
LMCI
Dementia
CSF abeta42
Amyloid Imaging
CSF Tau
FDG PET
MRI Hippocampal Volume
Cognitive Performance
Function (ADL)

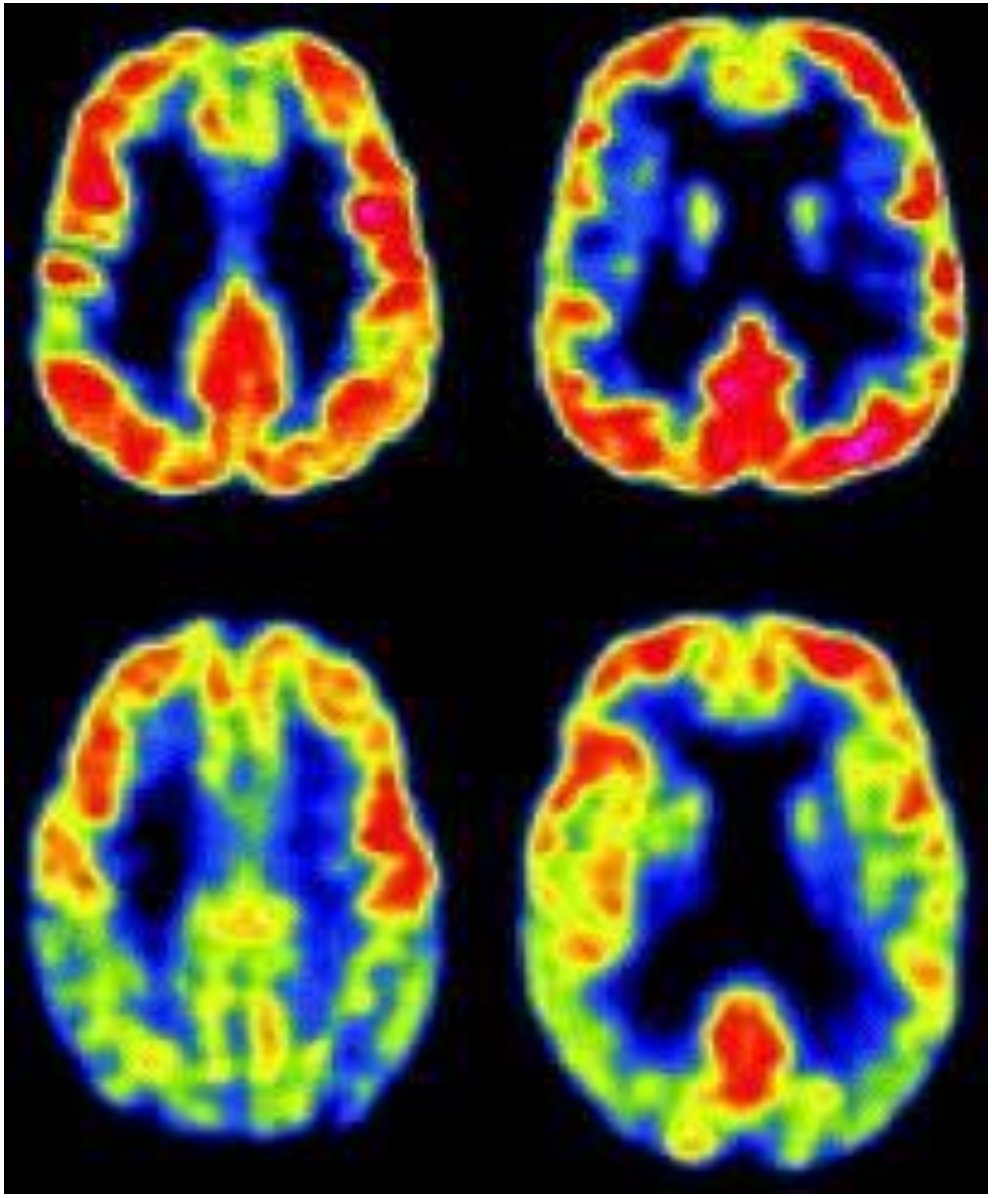
Amyloid PET in AD



Glucose PET Imaging to Rule in AD

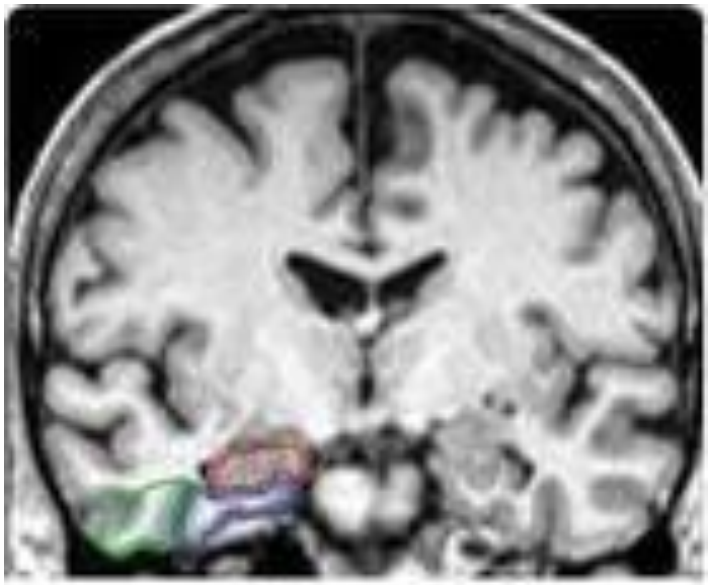
Normal

Alzheimer's Disease

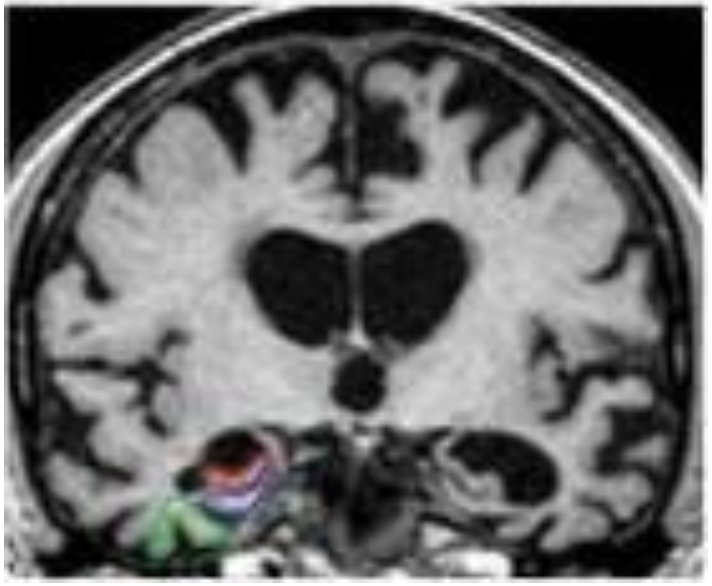


MRI to rule in Alzheimer's Disease

Normal
MTL volume



MTL Atrophy
in AD



2011: New Diagnostic Criteria for AD NIA-AA 2011

- Intended for both clinic and research settings
- Particular emphasis on biomarkers in the research setting
- Clinical trials initiated after 2011, began incorporating biomarkers into their protocols

Assessment of Amyloid Positivity in AD Clinical Trial Designs

- Initially, in substudies:
  - 50% in MCI studies and 25% in AD studies turned out not to have AD based on amyloid assessment!
- 2013: first clinical trial requiring all individuals to be amyloid positive (Lilly Expedition study)
- Since then, amyloid assessment is a standard requirement for enrolment in most trials

Value of Biomarkers in AD

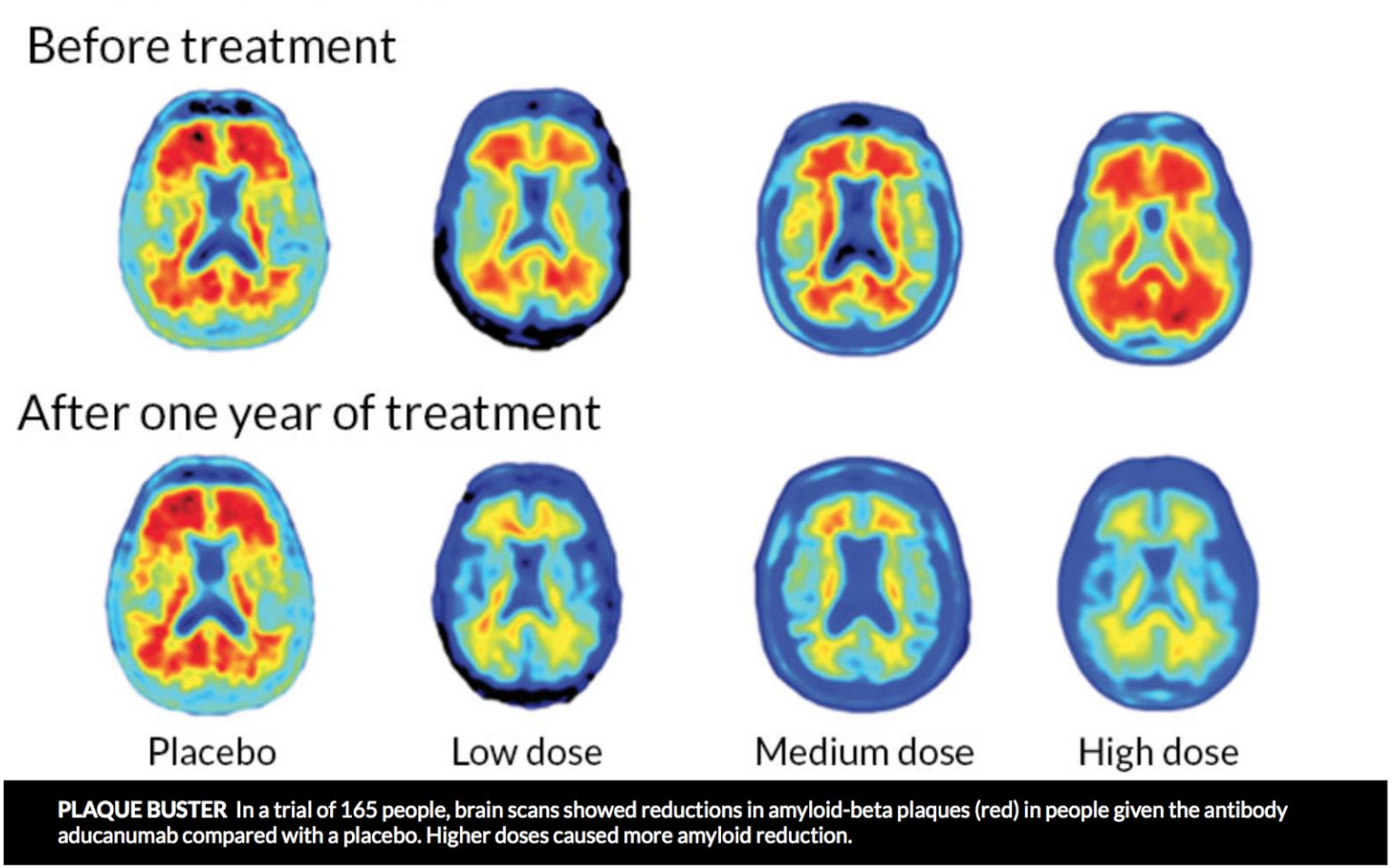
- Greater diagnostic certainty
- Early detection of disease
- Opportunity to intervene when symptoms are very mild or prior to symptoms
- Objective measures for disease monitoring
- Assess response to interventions
- Allow for prevention trials

Many Scenarios for which biomarkers can help clarify clinical profile

- Very mild patients
- Young patients
- Patients initially diagnosed with AD but not declining as expected
- Patients with non-amnestic presentations
- Patients with depression, concussion, other co-morbidities complicating the diagnosis


OUTLOOK
nature
THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE

Aducanumab Reverses Amyloid Plaque



PLAQUE BUSTER In a trial of 165 people, brain scans showed reductions in amyloid-beta plaques (red) in people given the antibody aducanumab compared with a placebo. Higher doses caused more amyloid reduction.

J. SEVIGNY ET AL/*NATURE* 2016

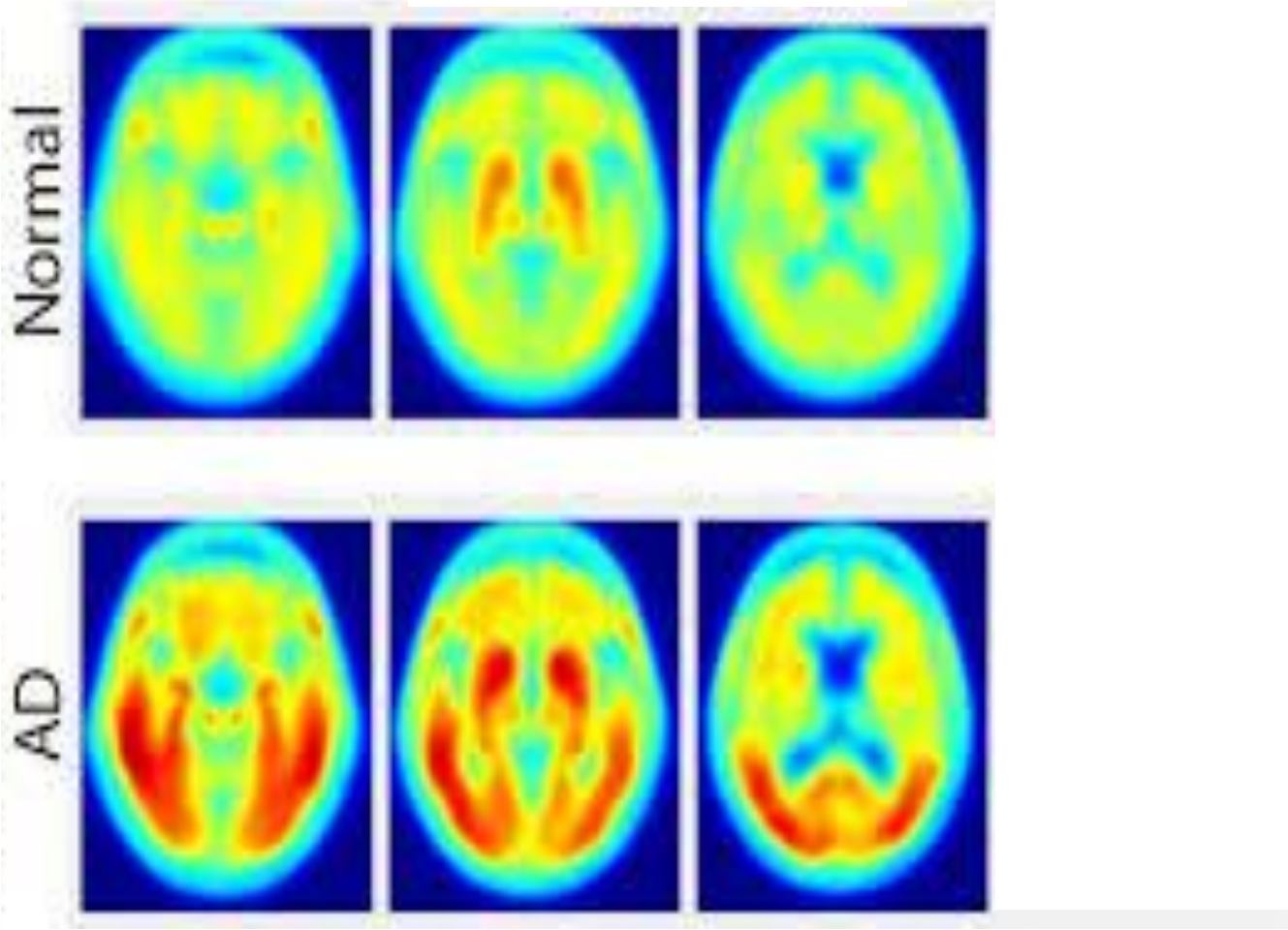
BAN 2401
Top Line Results AAIC July 25, 2018

- Dose dependent amyloid reduction
- Total amyloid clearance at top dose
- Reduction in tau as well
- 47% slowing of cognitive decline

Beyond 2011 Biomarkers: Accelerated Interest in Tau

- Tau PET tracers
  - bind tau in brain
  - spread of tau correlates with disease progression (unlike amyloid)
  - location of tau in brain correlates with symptoms (unlike amyloid)
- Anti-tau clinical trials
  - Ability to assess target engagement

Flortaucipir in AD



A/T/N Classification of AD

- Proposed in 2016: Clifford Jack et al
- 7 biomarkers used to describe the status of amyloid (A), tau (T), neurodegeneration (N)
- Binary determination for each of A/T/N
- Tau PET and CSF p-tau included in addition to the 5 biomarkers from the NIA-AA 2011
- Useful for disease staging (comparable to other diseases (e.g., TNM in cancer)

Newer Biomarkers in CSF and Plasma

- Neurogranin
  - A measure of synaptic injury
- Neurofilament light (Nf-L)
  - A measure of axonal injury
- Amyloid oligomers
  - May be the most injurious subtype of amyloid

EISAI BAN 2401
Biomarker Results: CTAD Oct 2018

- Each of 3 biomarkers measured in spinal fluid were consistent with disease slowing by BAN 2401
- Specifically, reductions seen in:
  - ✓ *pTau (marker of abnormal tau in AD)*
  - ✓ *Neurogranin (marker of synaptic damage)*
  - ✓ *Nf- L (marker of axonal degeneration)*

New FDA Guidance Jan 2018

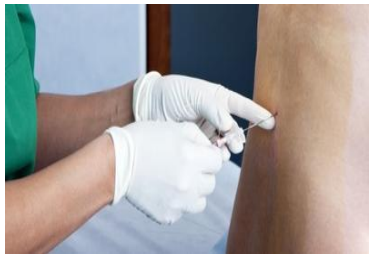
- For AD prevention studies, a change in a bio-marker may be considered a valid primary outcome measure if that change correlates with improvement in clinical outcome
- Opens the door to new trial designs and much shorter trials (months rather than years)

Present Availability of AD Biomarkers For Clinical Use

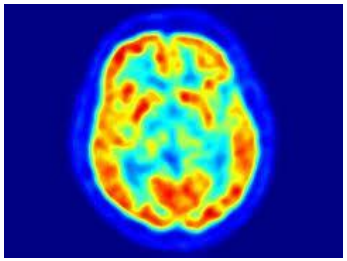
- Spinal fluid biomarkers (CSF amyloid, tau) are gov. funded in Canada
- 3 amyloid PET tracers available in the USA for clinic use (not covered by Medicaid)
- 1 amyloid tracer approved in Canada in 2017 (cost coverage challenging)
- Clinical use criteria: 1. symptoms present and 2. biomarker result will alter care

Need for Accessible and Affordable AD Biomarkers

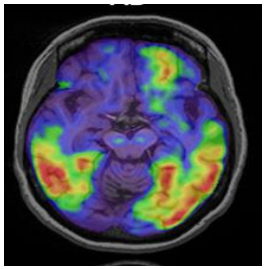
Advances in biomarkers over past 20 years



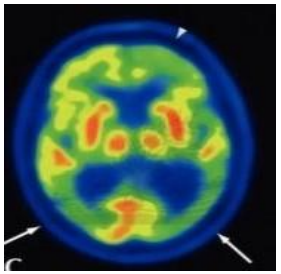
CSF analysis



Amyloid PET



Tau PET



FDG PET

IMPLEMENTATION:

Research	Memory Clinic	Primary Care	Pop Screening
YES	YES (some)	NO	NO

Blood Based Biomarker for AD

- The Holy Grail of biomarkers for AD
- Elusive for so long but becoming a reality
- Bateman July 2017 (AAIC): amyloid measured by mass spectrometry approach appears sensitive and specific for identifying AD
- Other labs employing other techniques
- Alzheimer's blood test should be available in the next few years!

Recap of Diagnostic Criteria for AD

- 1906: Dr. Alois A. describes first case of AD
  - Dx, thereafter, based on autopsy (brain plaques & tangles)
- 1984: NINCDS-ADRDA “McKhann” criteria
  - Dx based on clinical criteria (hx, exam, ruling out other ds)
  - Assumes: AD=dementia; age 40-90; memory loss dominates
- 2011: NIA-AA criteria
  - Recognizes AD spectrum: pre-symptomatic, MCI, dementia
  - Incorporates 5 biomarkers to enhance diagnostic certainty
- 2016: A/T/N
  - Allows for staging of AD pathology by 7 biomarkers

Do Not Doubt Progress in AD

- AD is diagnosable in life and can be staged biologically
- Trial populations can be accurately enrolled and interventions evaluated objectively and biologically
- New biomarkers are emerging including blood-based biomarkers
- Population screening will be a feasible once minimally invasive biomarkers are available and this screening will be desirable once DMT are available

Questions