Blood biomarkers for Alzheimer's disease in current practice

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The Memory Hub

A D R C
Alzheimer's Disease Research Center

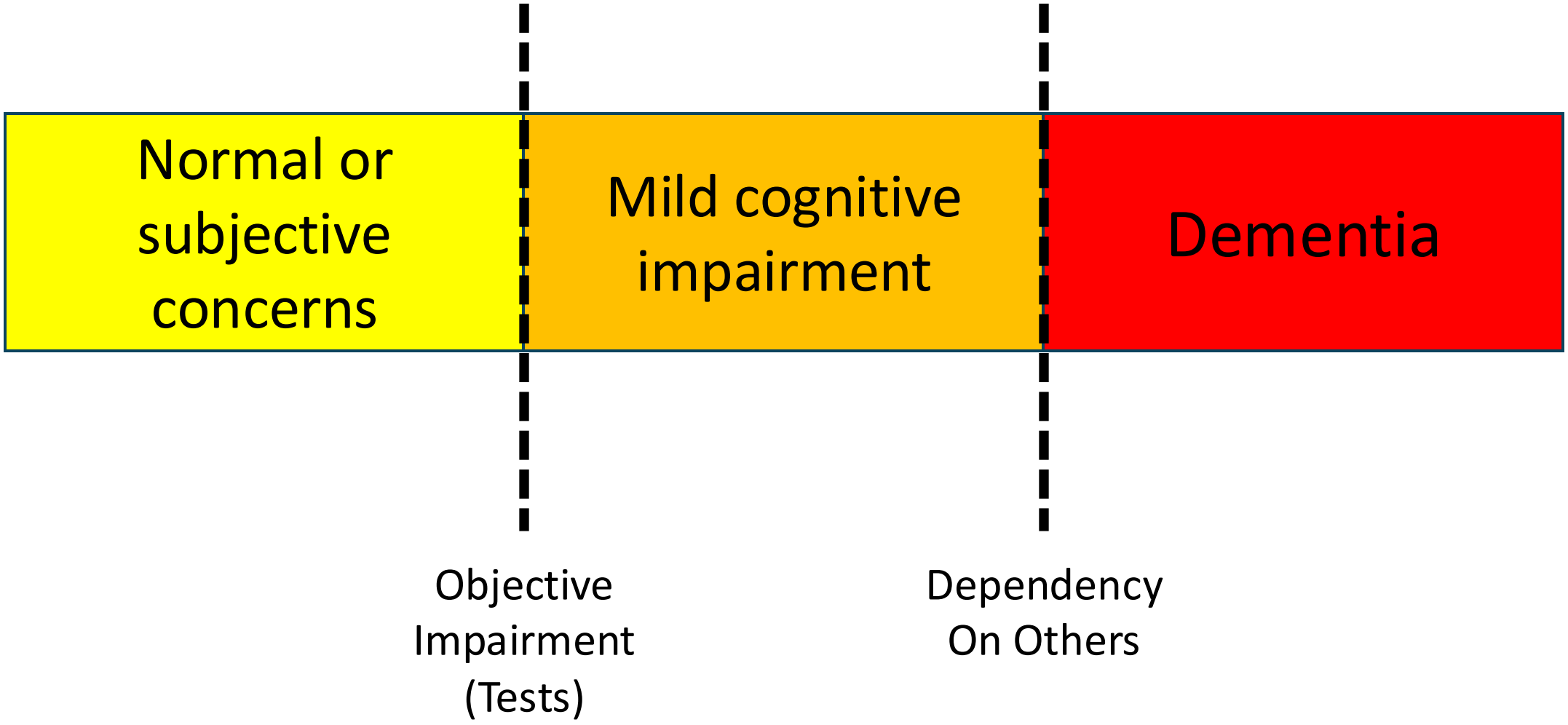
Disclosures

- Dr. Grabowski receives federal funding from NIH for leading the Alzheimer's Disease Research Center, and related grants
- Dr. Grabowski has no financial relationship to entities that manufacture, or market biomarkers or pharmacologic treatments of Alzheimer's disease and related dementias.

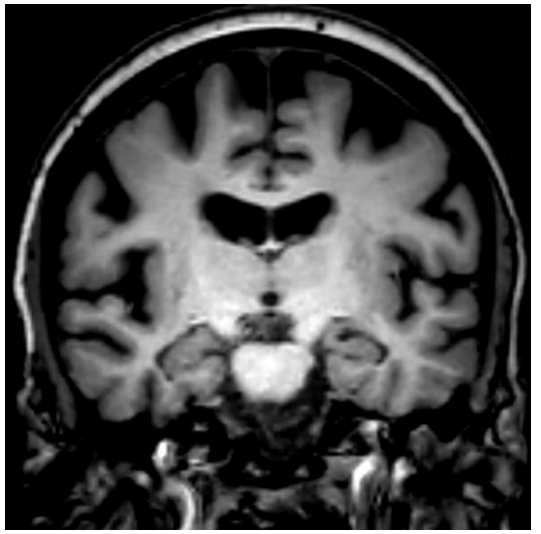
Objectives

- Understand the basis of blood biomarker testing for Alzheimer disease (AD)
- Understand the importance of establishing complaint and cognitive impairment in assessment of memory in primary care
- Understand the utility of AD blood biomarkers
- Understand limitations of AD blood biomarkers
- Understand current practice recommendations for AD blood biomarkers

Cognitive diagnosis
”What’s wrong with memory and thinking”



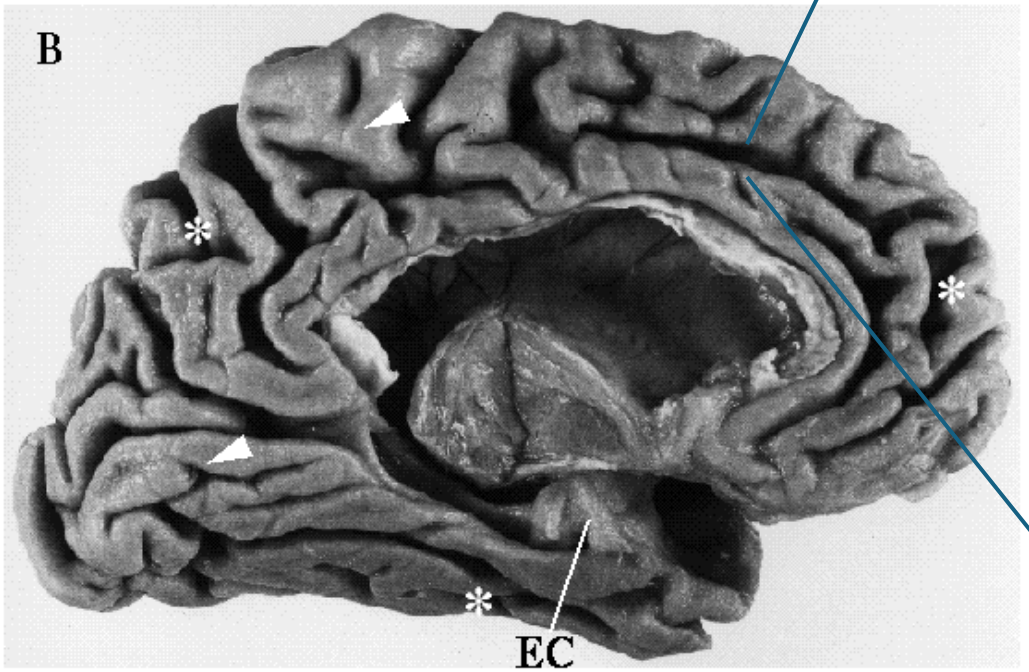
Case 1



- 76 year old woman
- CC: Short term memory is not great
- Retired attorney, aware of trouble remembering directions, or whether she has talked to somebody that day or not. Daughter says “for 2-3 yrs every conversation she says something that she has already told me”
- Hypertension, hyperlipidemia
- MoCA 28/30, normal neurological exam
- Two years later, MoCA 23/30

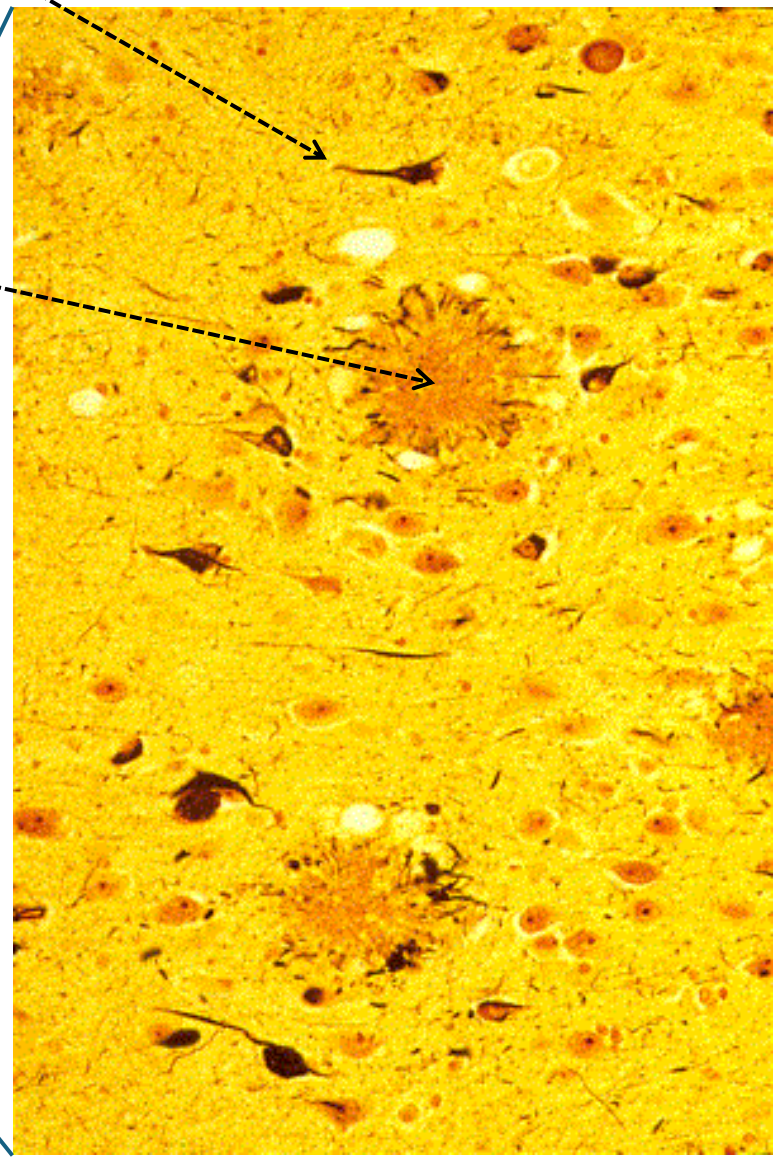
Causal diagnosis
”What’s wrong with the brain”
(If you could look under the microscope)

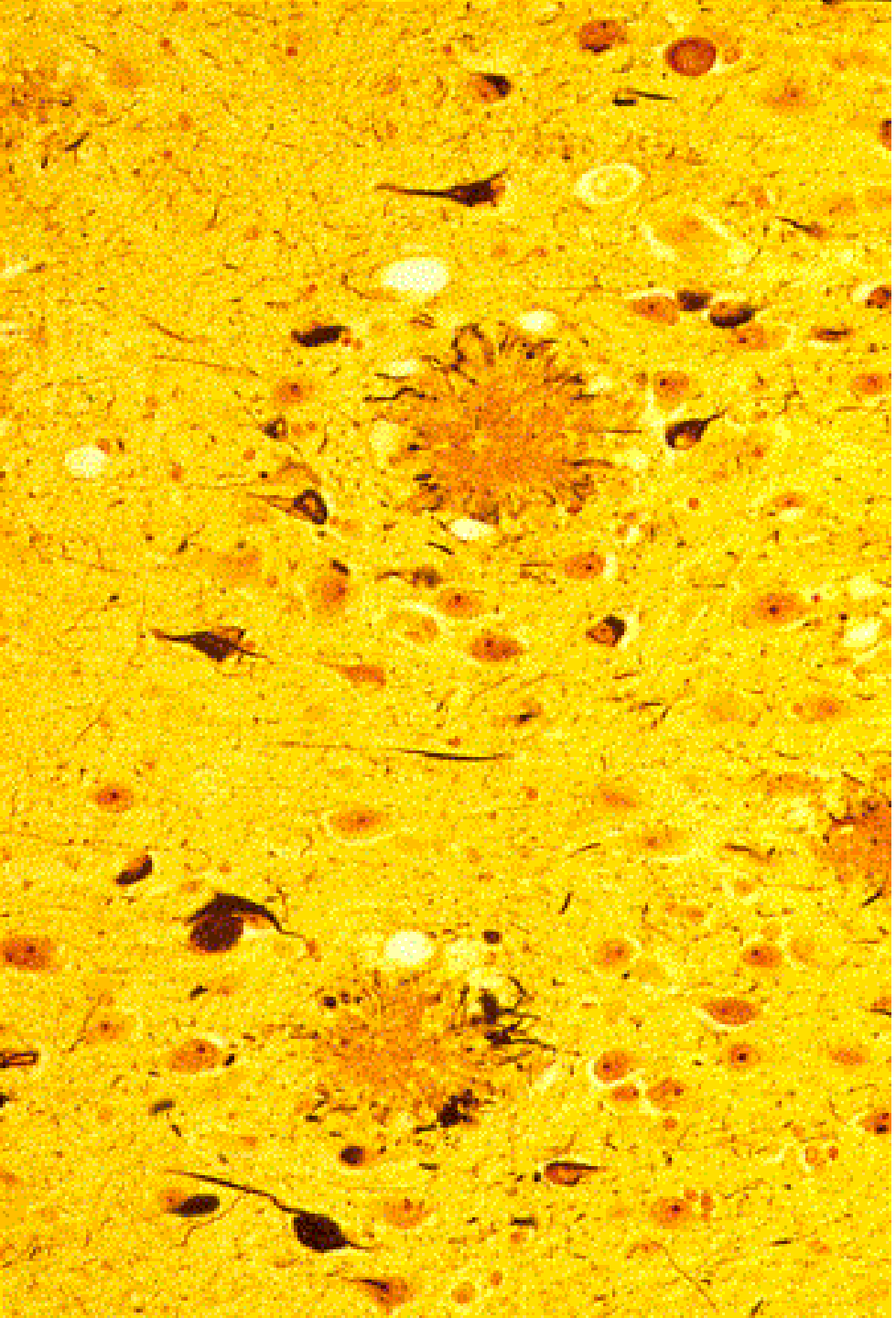
Alzheimer’s disease



Tau Tangles.

Amyloid
Plaques



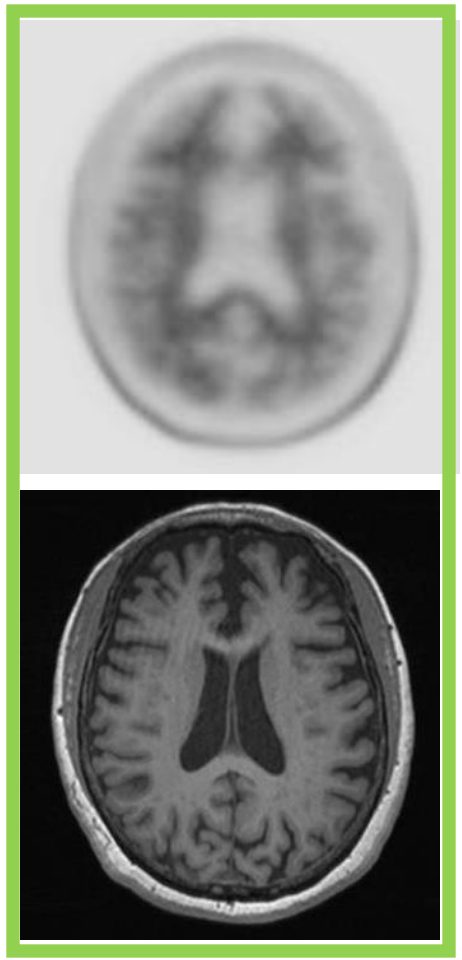


Importance of amyloid plaques and tau tangles

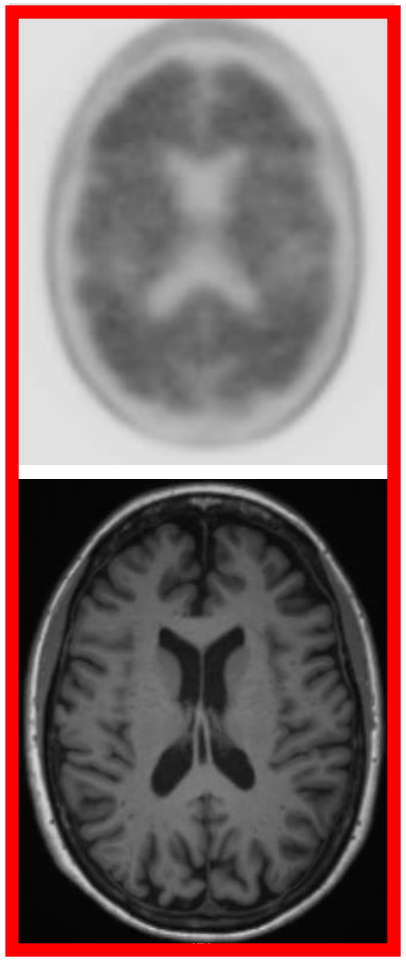
- Defining hallmarks of Alzheimer's disease
- Ways to detect and measure AD (biomarkers)

Amyloid PET scans - revolutionary

NEGATIVE – NOT ALZHEIMER'S



POSITIVE – ALZHEIMER'S PLAQUES



Visual Read

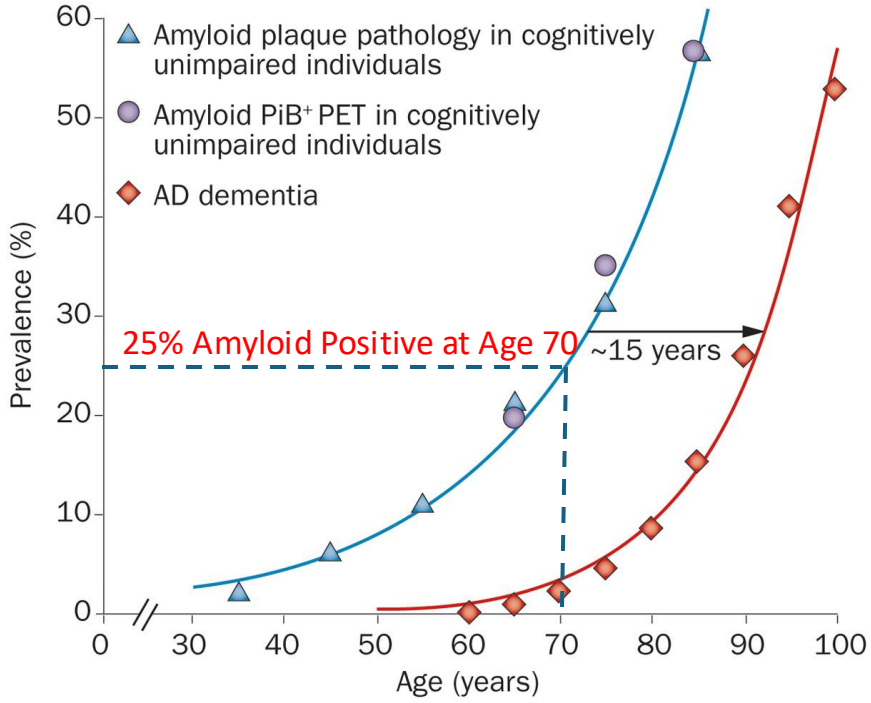
Or

Quantitative Read

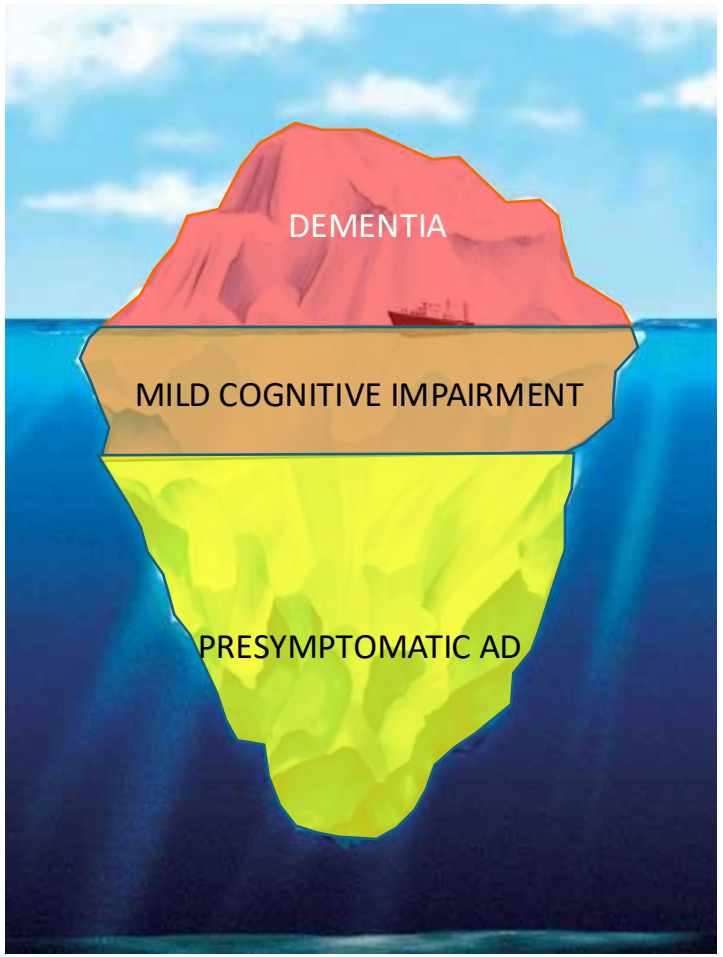
22 centiloids – abnormal
100 centiloids – typical AD dementia

Moderate density of plaques
Alzheimer's pathophysiology
is present

Gold standard in vivo diagnosis



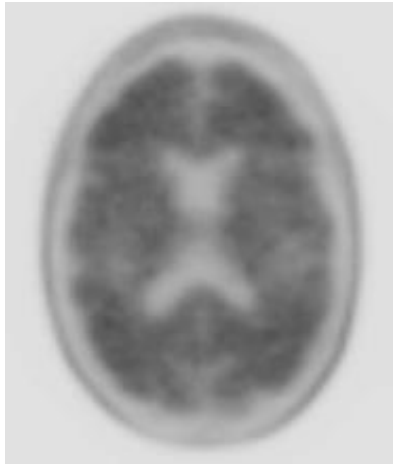
Langbaum, J. B. *et al.* (2013) Ushering in the study and treatment of preclinical Alzheimer disease *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2013.107



ALZHEIMER'S DISEASE FLUID BIOMARKERS

- Cerebrospinal Fluid
  - Ab42
  - Ab42/Ab40 ratio
  - 181-p-tau/AB42 ratio
- Blood plasma
  - 181-p-tau
  - 217-p-tau/Ab42 ratio
  - 217-p-tau
  - 217-p-tau/np-tau

90%
Accuracy



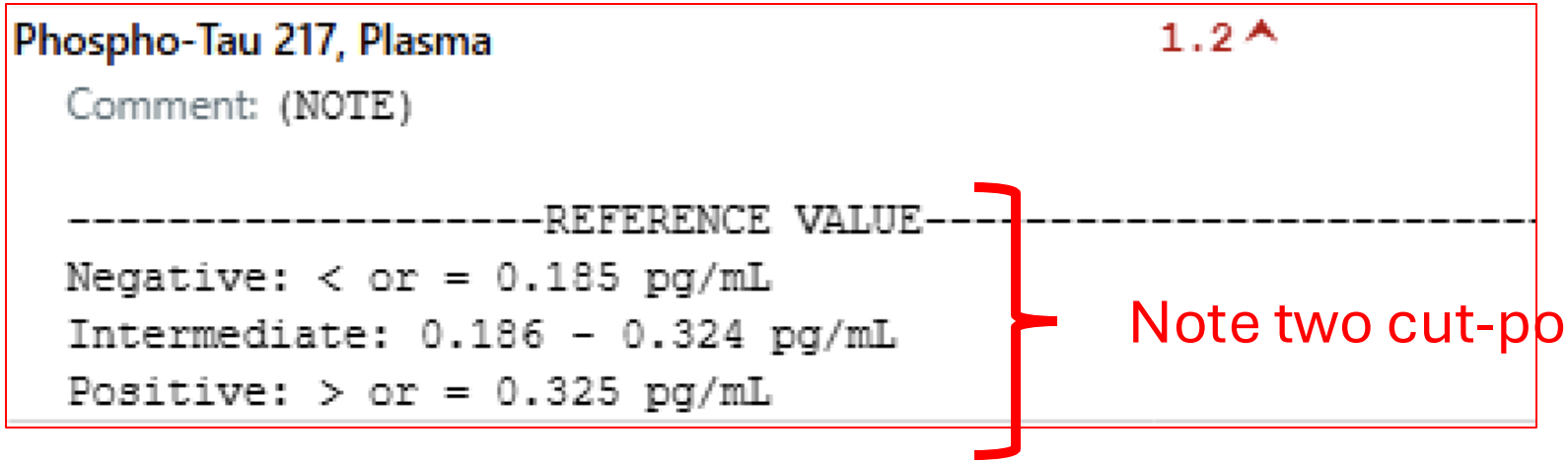
Moderate density of plaques

Alzheimer's pathophysiology is present

Gold standard
Useful to confirm diagnosis

Back to Case 1

- She has a plasma 217-p-tau test



Supports the presence of Alzheimer's pathophysiology

Diagnosis is amnestic mild cognitive impairment due to underlying AD

Two years into her course when lecanemab became available, this patient qualified

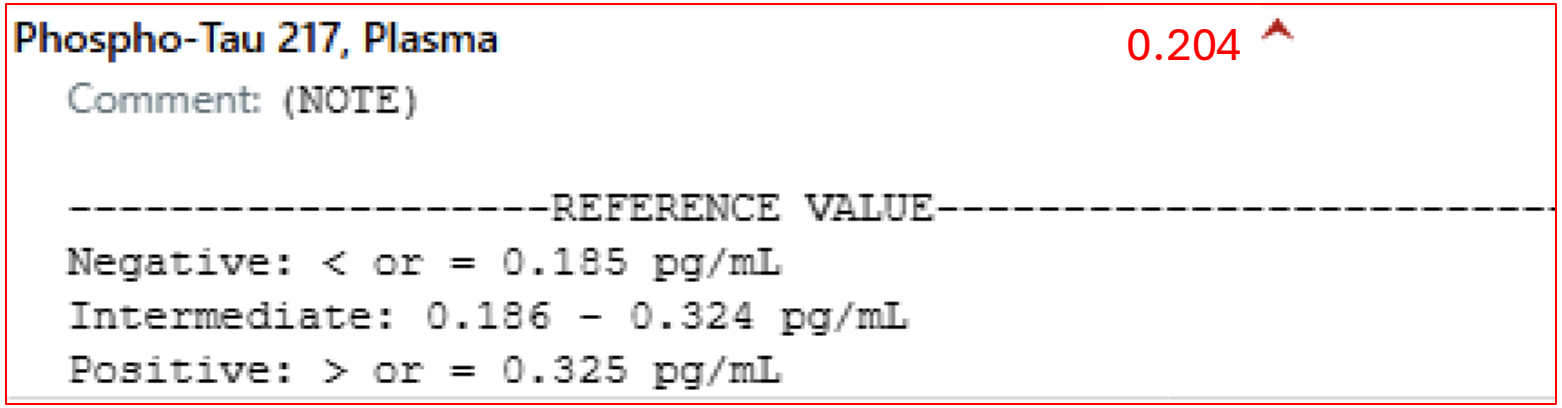
Advantages of biomarkers

- Early diagnosis
- Aligning treatment and mechanism
- Clarification of atypical cases

Diagnostic Biomarker

Case 2

- 76 years old
- CC: trouble sleeping, forgets why he goes on errands, mother had dementia
- Retired manager
- Hypertension, hyperlipidemia, obesity, chronic kidney disease
- Plasma 217-p-tau



Limitations

- AD diagnostic biomarkers turn positive years before impairment
- AD diagnostic biomarkers are not actionable in the absence of cognitive impairment
- Accuracy of blood biomarkers has been assessed in the specialty setting and not in primary care
- Available blood markers are not able to estimate disease burden or track progression and treatment
- AD commonly occurs with other brain pathology, especially small vessel vascular disease and Lewy body pathology, and blood markers do not assess the presence or relative importance of these pathologies
- Elevation of plasma markers can occur in the setting of renal disease

Case 2

- Plasma markers are not appropriate in the absence of documented cognitive impairment
- Intermediate results or results near the cutpoint will need confirmatory testing
- Plasma markers can be elevated in renal disease

When *is* a biomarker result actionable?

- Diagnostically, in evaluating atypical presentations
  - Non-amnestic presentations, rapid progression, etc
- Therapeutically, in qualifying an AD patient for one of the new monoclonal antibody treatments
  - These are indicated for MCI or very mild dementia only
  - These treatments have a serious side effect risk (ARIA)
- In both cases, as part of a comprehensive diagnostic evaluation in setting of established cognitive impairment

AA Clinical Practice Guideline 2025

R1 — In patients with objective cognitive impairment presenting for specialized memory-care use a high-sensitivity BBM test as a **triaging test** in the diagnostic workup of Alzheimer's disease.

R2 — In patients with objective cognitive impairment presenting for specialized memory care, use high-sensitivity and high-specificity BBM test as a **confirmatory test** in the diagnostic workup of AD

Good Practice Statement — A BBM test should not be obtained before a comprehensive clinical evaluation by a health care professional, and test results should always be interpreted within the clinical context.

Conclusions

- Blood plasma AD biomarkers make AD testing much more accessible but are not actionable on their own
- Blood biomarker tests should be undertaken after the establishment of a complaint and cognitive impairment and as a part of a comprehensive workup
- In the appropriate setting blood biomarkers can confirm AD diagnosis and candidacy for antiamyloid therapy
- Expect evolution of this area of medicine, particularly if clinical trials demonstrate efficacy in preclinical AD