Blood Tests for Alzheimer's Disease and Dementia: A Caregiver's Guide

No conflicts to disclose

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MALVERN, PA, and TOKYO, JAPAN, May 16, 2025—Fujirebio today announced that the U.S. Food and Drug Administration (FDA) has granted 510(k) clearance for the company's Lumipulse® G pTau 217/β-Amyloid 1-42 Plasma Ratio in-vitro diagnostic (IVD) test for the assessment of amyloid pathology in patients being evaluated for Alzheimer's disease and other causes of cognitive decline. The test, which was granted Breakthrough Device Designation by the FDA, is the first FDA cleared blood-based IVD test in the U.S. to aid to identify patients with amyloid pathology associated with Alzheimer's Disease (AD).

The Lumipulse G pTau 217/β-Amyloid 1-42 Plasma Ratio test is an accurate, minimally invasive, accessible measurement of pTau 217 and β-Amyloid 1-42 concentrations in plasma as a proxy for the presence of β-Amyloid plaque pathology in the brain. It is intended for use in adult patients aged 50 years and older presenting at a specialized care setting with signs and symptoms of cognitive decline. In a clinical study population of 499 patients, which closely mirrored the US demographics, and when applying a dual cut point, the test demonstrated a positive predictive value (PPV) of 92%, a negative predictive value (NPV) of 97% with only 20% patients who are uncertain to have amyloid pathology, thus requiring further testing.

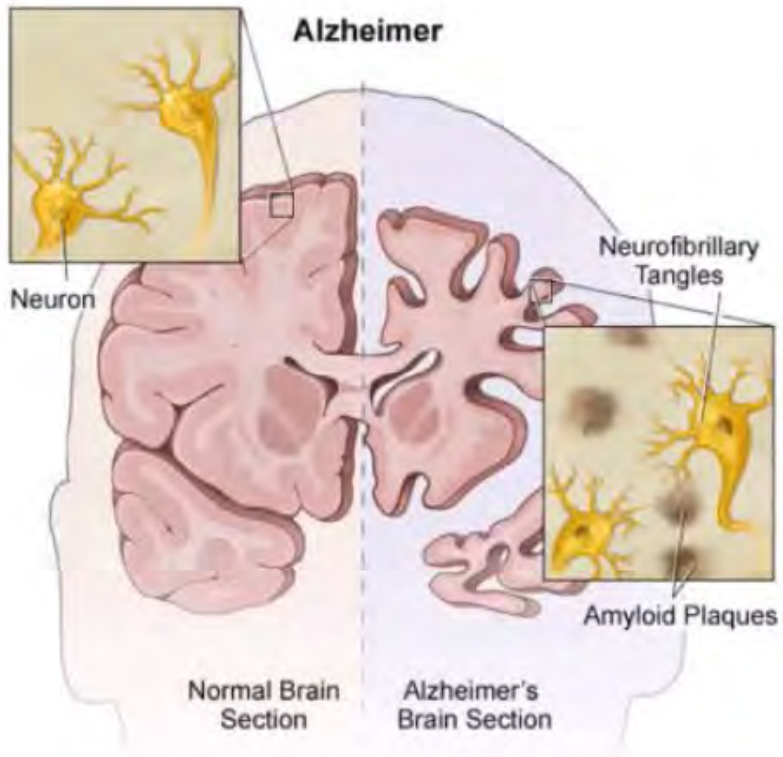
Roche's Elecsys® pTau181 becomes the only FDA-cleared blood test for use in primary care to rule out Alzheimer's-related amyloid pathology

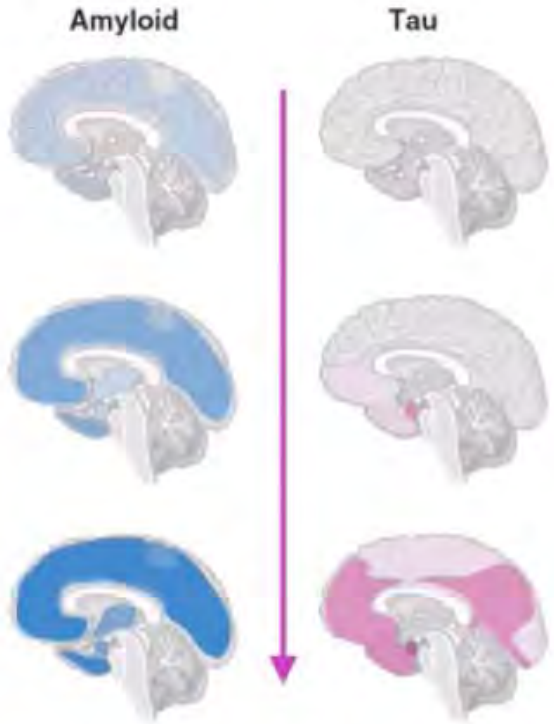
Basel, October 13, 2025 – Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that the United States Food and Drug Administration (FDA) has cleared its Elecsys pTau181 test, the only blood-based biomarker (BBM) test indicated as an aid in the initial assessment for Alzheimer's disease and other causes of cognitive decline in the primary-care setting. The Elecsys pTau181 test is intended for patients ages 55 and older presenting with signs, symptoms or complaints of cognitive decline. It measures phosphorylated Tau (pTau) 181 protein in human plasma, a key biomarker for Alzheimer's pathology, including amyloid plaque and tau aggregate pathology.

Alzheimer's Disease

AD Pathology

- Characterized most notably by aggregates of misfolded proteins
  - Extracellular deposition of ß-amyloid (Aß) in the form of neuritic plaques
  - Aggregations of hyperphosphorylated tau protein in the form of intraneuronal neurofibrillary tangles (NFTs)
- Results in synapse loss and neuronal atrophy predominately throughout the cerebral cortex





The spread of amyloid and tau pathology throughout the brain during AD. Sheppard, O., & Coleman, M.P. (2020). Alzheimer's Disease: Etiology, Neuropathology and Pathogenesis. *Alzheimer's Disease: Drug Discovery.*

1. Long JM, Holtzman DM. Alzheimer Disease: An Update on Pathobiology and Treatment Strategies. 2019. 2. Sheppard O, Coleman M. Alzheimer's Disease: Etiology, Neuropathology and Pathogenesis. 2020.

DSM-5-TR, 2022

First, criteria for Major NCD must be met:

- Evidence of significant cognitive decline in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition), based on concern from the individual, a knowledgeable informant, or clinician, and preferably documented by standardized testing or quantified clinical assessment.
- Cognitive deficits interfere with independence in everyday activities.
- Not occurring exclusively during delirium.
- Not better explained by another mental disorder.

Additional features for “due to AD”:

- Insidious onset and gradual progression of impairment.

Probable vs Possible (Major NCD):

- Probable AD is diagnosed if either:
  - Evidence of a causative Alzheimer’s disease genetic mutation from genetic testing or a strong family history; OR
  - All three of the following are present:
    a) Clear evidence of decline in memory and learning and at least one other cognitive domain (by history and/or serial neuropsychological testing).
    b) Steadily progressive, gradual decline in cognition, without extended plateaus.
    c) No evidence of mixed etiology (i.e., absence of other significant contributing neurological, cerebrovascular, mental, or systemic conditions).
- Possible AD is diagnosed if the clinical criteria are met but the course is atypical (e.g., not a clearly amnestic presentation or not steadily progressive) or there is evidence of a mixed etiology (coexisting conditions that could contribute to the cognitive decline), and there is no confirmed AD-causing mutation.

NIA–AA research framework and 2024 revision (biological definition, AT(N)): 2024

- Concept: AD is defined biologically by biomarkers rather than by symptoms alone. Biomarkers are grouped as:
  - A (amyloid pathology): CSF Aβ42/40, amyloid-PET; increasingly, plasma Aβ42/40 (mass spectrometry) used for screening.
  - T (tau pathology): CSF p-tau or tau-PET; plasma p-tau (especially p-tau217) is increasingly supported for T.
  - (N) neurodegeneration: MRI atrophy, FDG-PET hypometabolism, CSF/plasma NfL; used for staging/severity, not to define AD by itself.
- Classification (common across 2018 and the 2024 revision):
  - Alzheimer’s pathologic change: A+ only (T−).
  - Alzheimer’s disease (biological AD): A+ and T+ (regardless of symptoms).
- What’s “new”: The 2024 revision (proposed by NIA–AA/Alzheimer’s Association) updates acceptable biomarker modalities, explicitly acknowledges high-performing blood tests (e.g., p-tau217, plasma Aβ42/40 by MS) as part of workflows (often as triage) and refines staging/terminology for clinical and research use.

Jack CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimer's Dement. 2024;20:5143–5169. **https://doi.org/10.1002/alz.13859**

International Working Group (IWG) criteria (clinical + biological confirmation): 2022-2024

- Concept: A diagnosis of AD requires both (a) a characteristic clinical phenotype (typical amnestic or recognized atypical variants) and (b) pathophysiological biomarker evidence of both amyloid and tau pathology.
- Biomarker requirements:
  - Amyloid: positive amyloid-PET or CSF Aβ42/40 abnormality (A+).
  - Tau: elevated CSF p-tau or tau-PET positivity (T+).
  - Blood biomarkers: increasingly promising (e.g., p-tau217) but generally considered supportive; many IWG statements still prioritize CSF/PET for definitive diagnosis.

Dubois B, Villain N, Schneider L, et al. Alzheimer Disease as a Clinical-Biological Construct-An International Working Group Recommendation. JAMA Neurol. 2024 Dec 1;81(12):1304-1311..

PLASMA AD BIOMARKERS



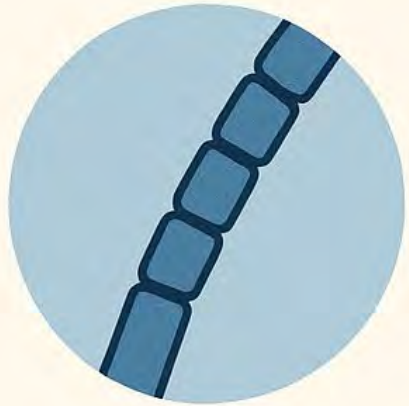
p-tau

phosphorylated tau



Aβ42

amyloid β42



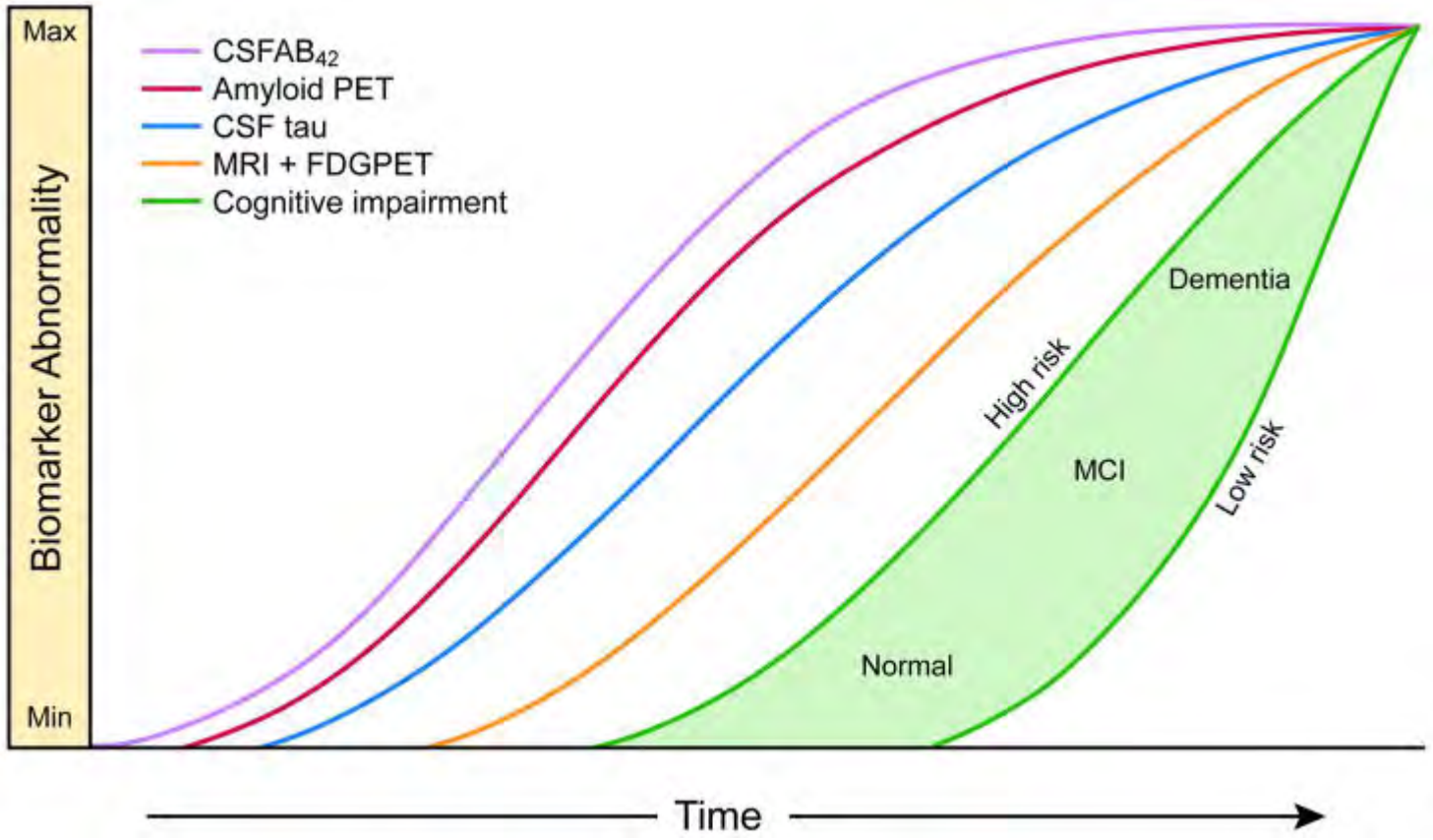
NfL

neurofilament light

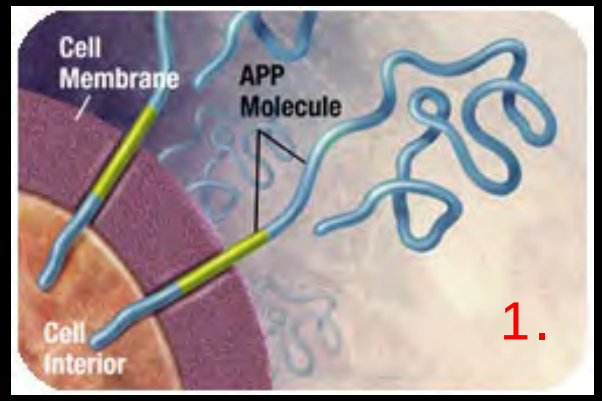


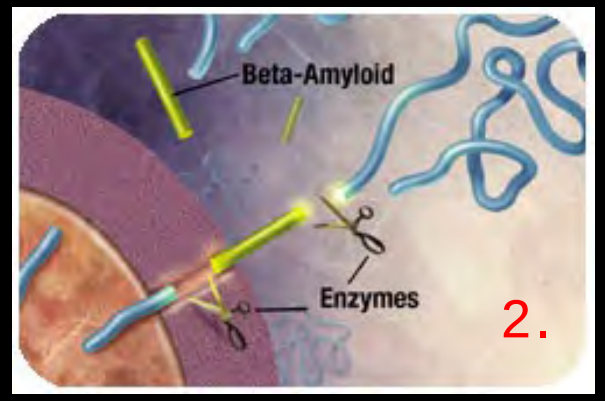
GFAP

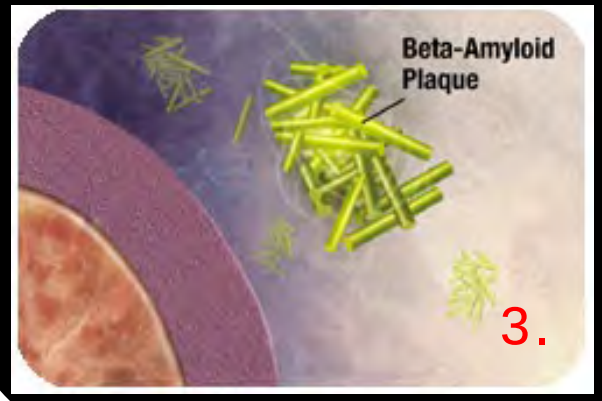
glial fibrillary acidic protein



Trojanowski, Lancet Neurology 2013





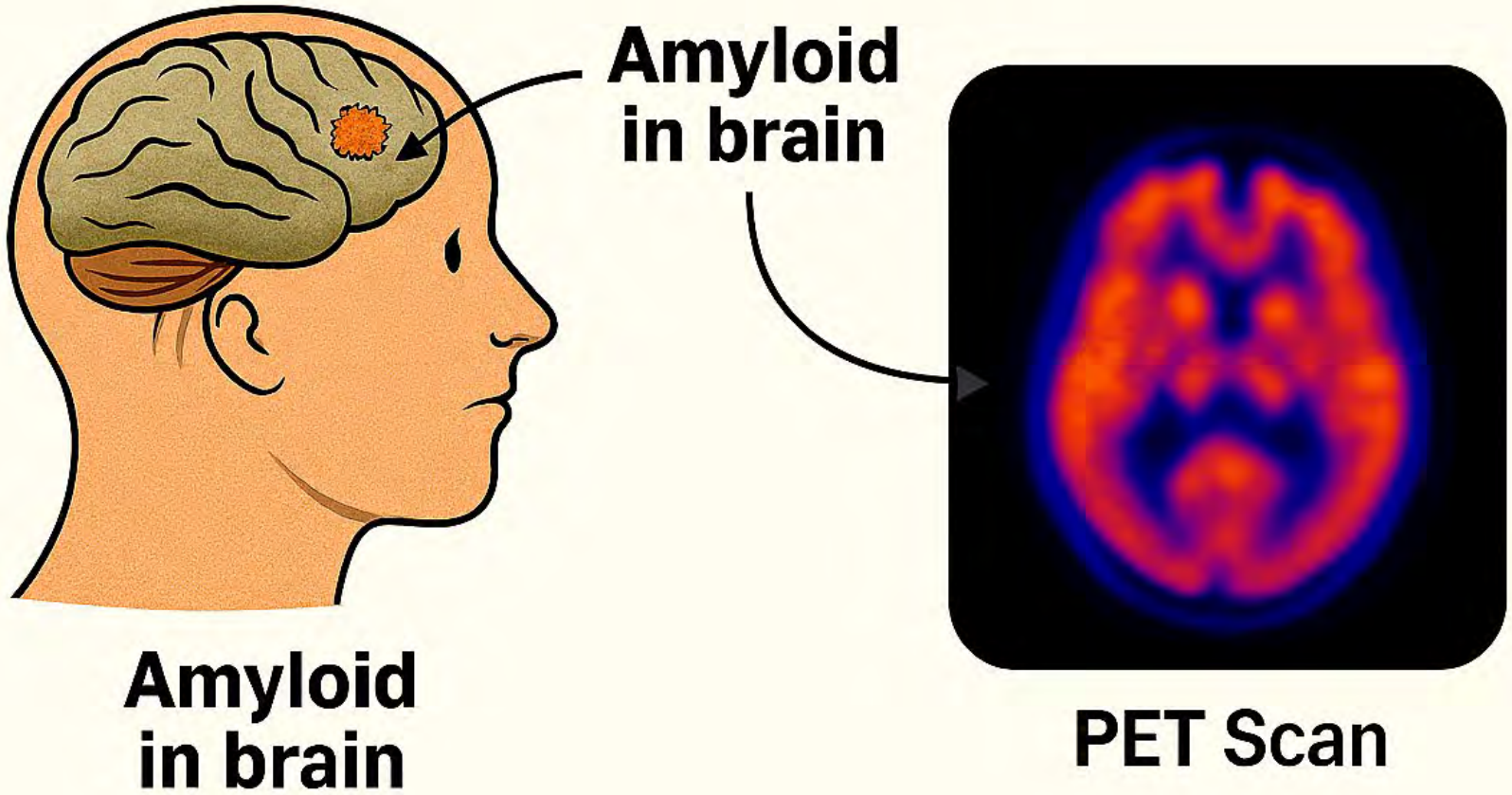


Amyloid precursor protein (APP) is the precursor to amyloid plaque.

1. APP sticks through the neuron membrane.
2. Enzymes cut the APP into fragments of protein, including beta-amyloid.
3. Beta-amyloid fragments come together in clumps to form plaques.

Detecting Amyloid in the Brain

Brain PET Scan



Clinically (FDA) approved amyloid PET ligands to visualize amyloid plaques:

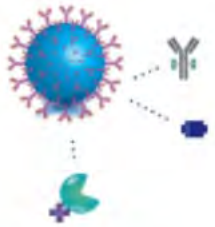
Florbetapir (Amyvid)

Florbetaben (Neuraceq)

Flutemetamol (Vizamyl)

1

Paramagnetic particles coupled with antibodies designed to bind to specific targets are added to the sample.



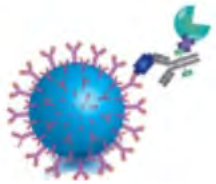
2

Detection antibodies – capable of generating fluorescent product – are added.



3

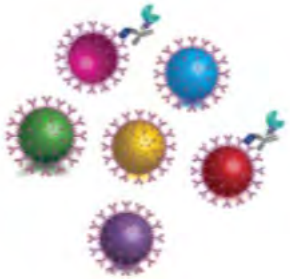
The objective is to form an immunocomplex consisting of the bead, bound protein, and detection antibody.



SiMOA

4

At low concentrations, each bead will contain one bound protein, or none.



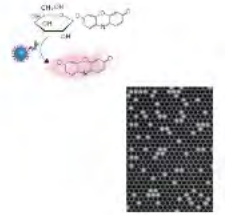
5

The sample is loaded into arrays, in the Simoa disc, consisting of more than 200,000 microwells – each large enough to hold one bead.



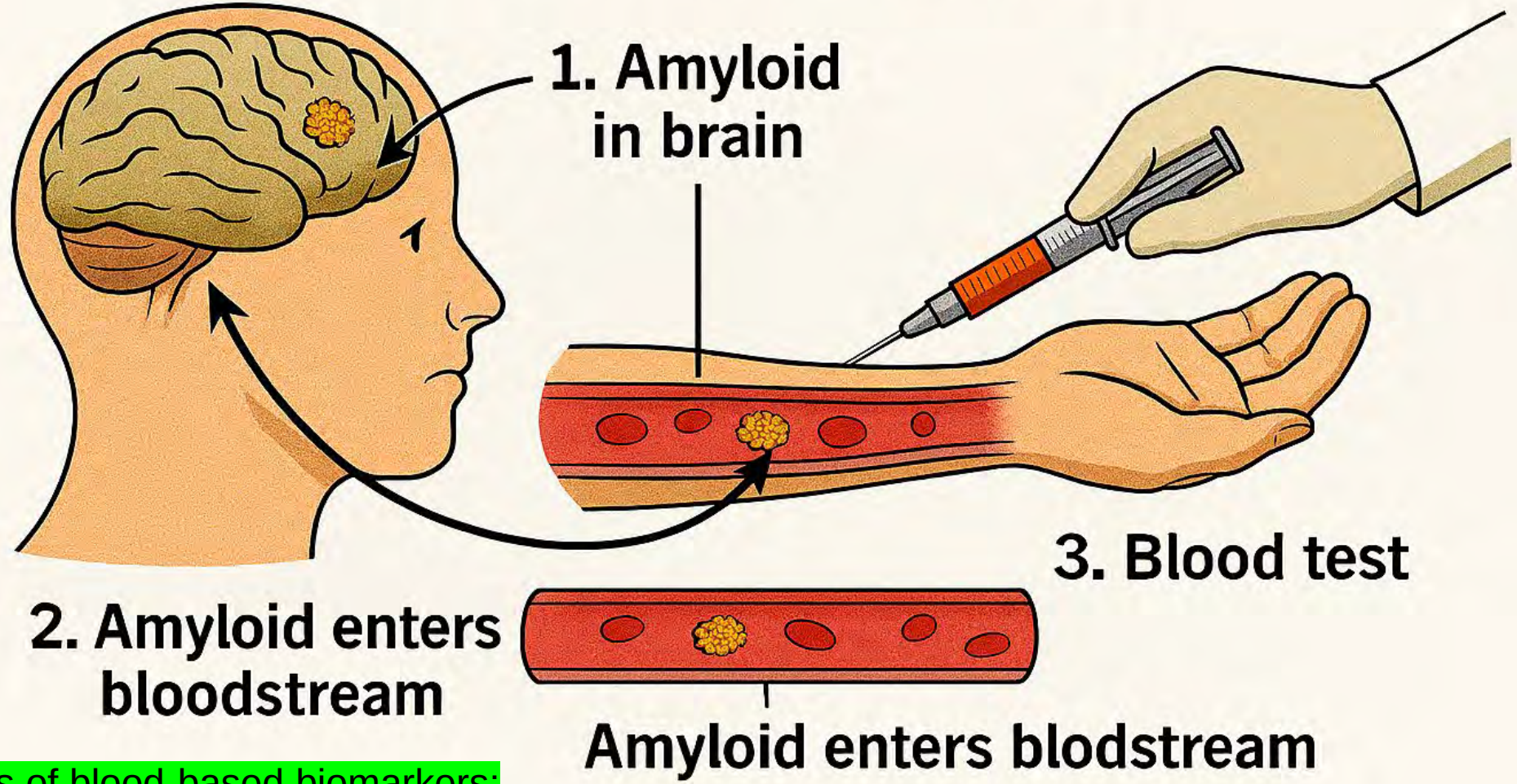
6

Enzymatic signal amplification with fluorescent substrate, fluorescence imaging and data reduction.



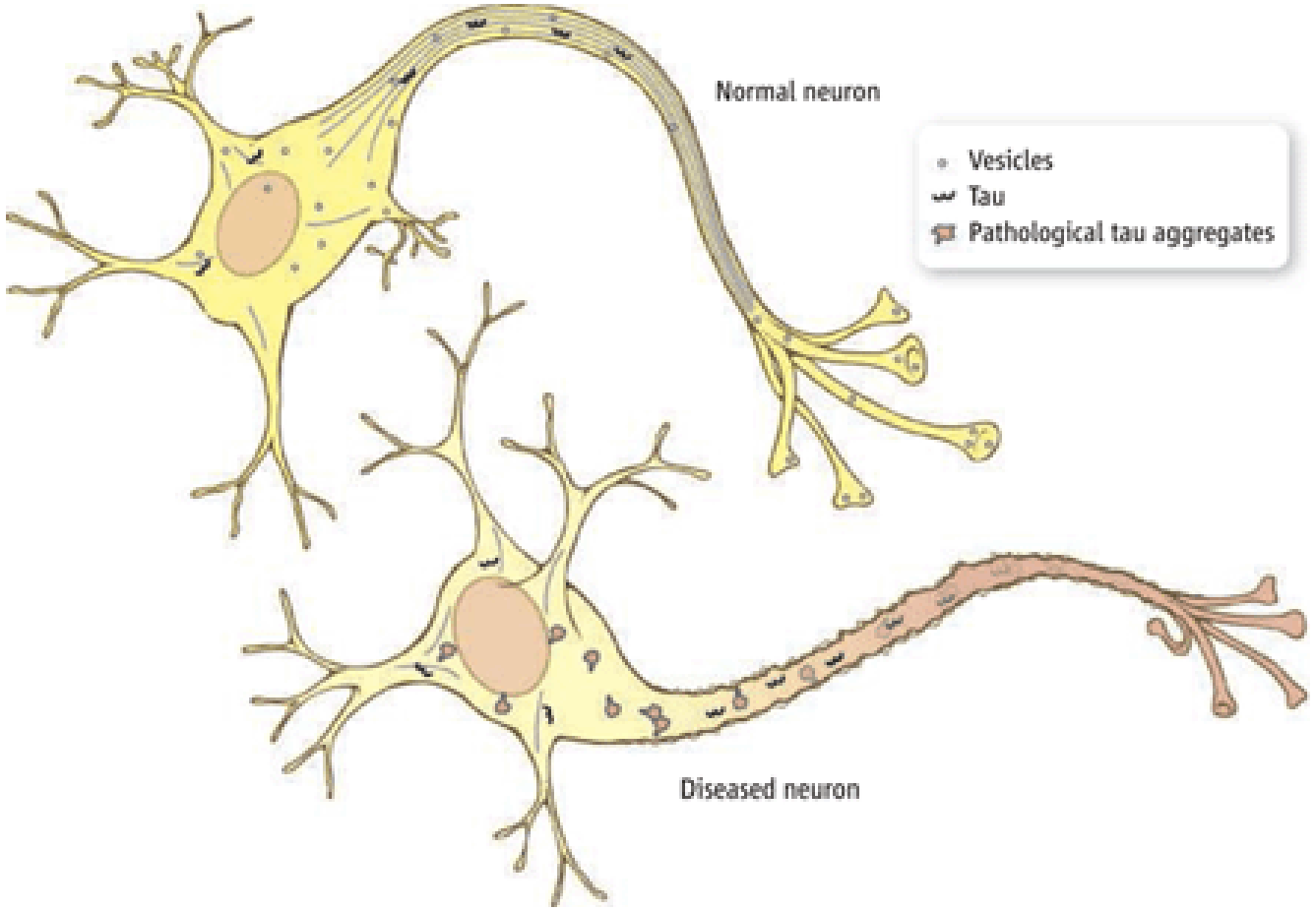
Detecting Amyloid in the Brain

Alzheimer's Disease Diagnostics



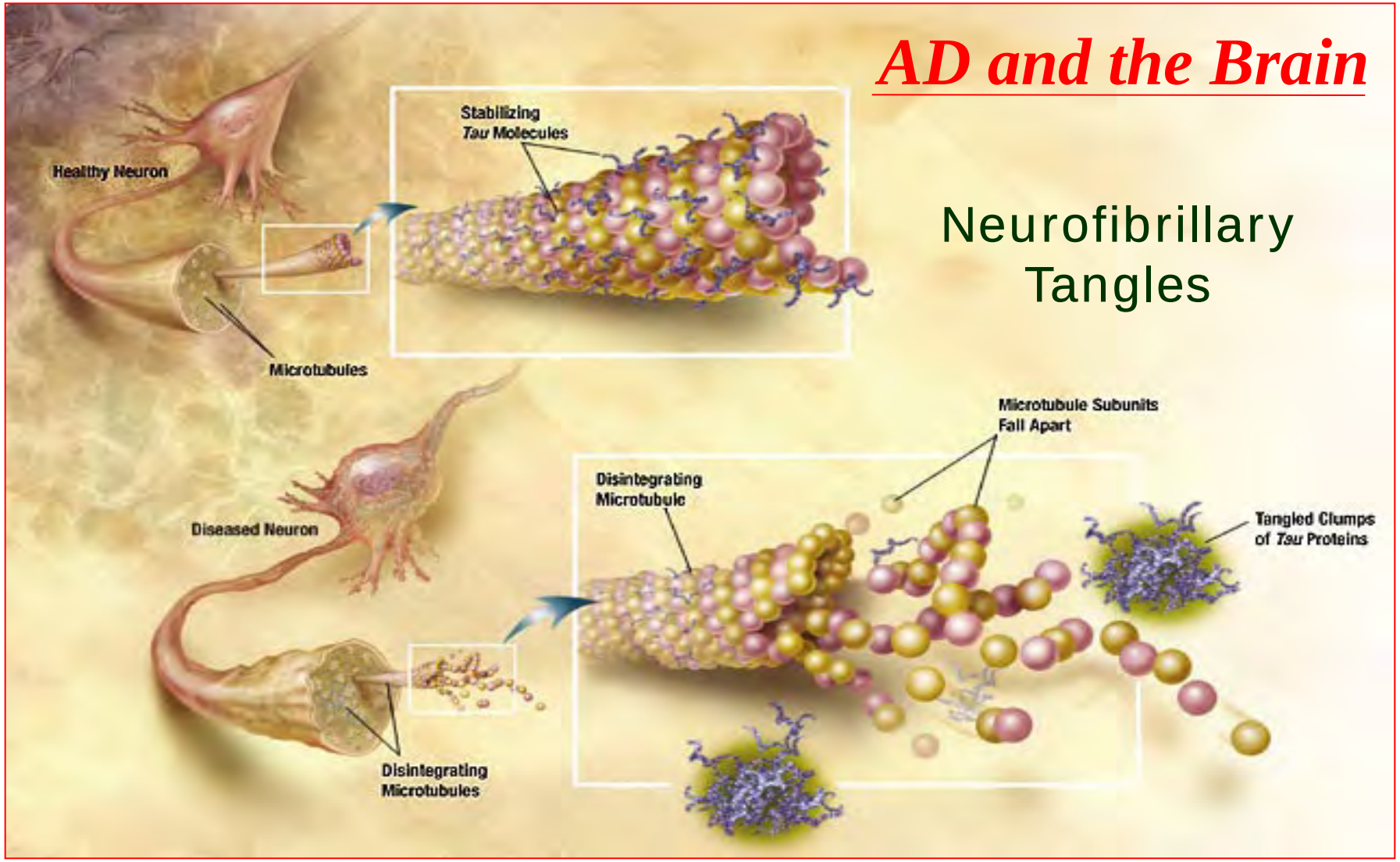
Limitations of blood-based biomarkers:

Low soluble concentrations, peripheral sources of proteins, amyloid can bind to blood cells, and renal clearance can affect levels

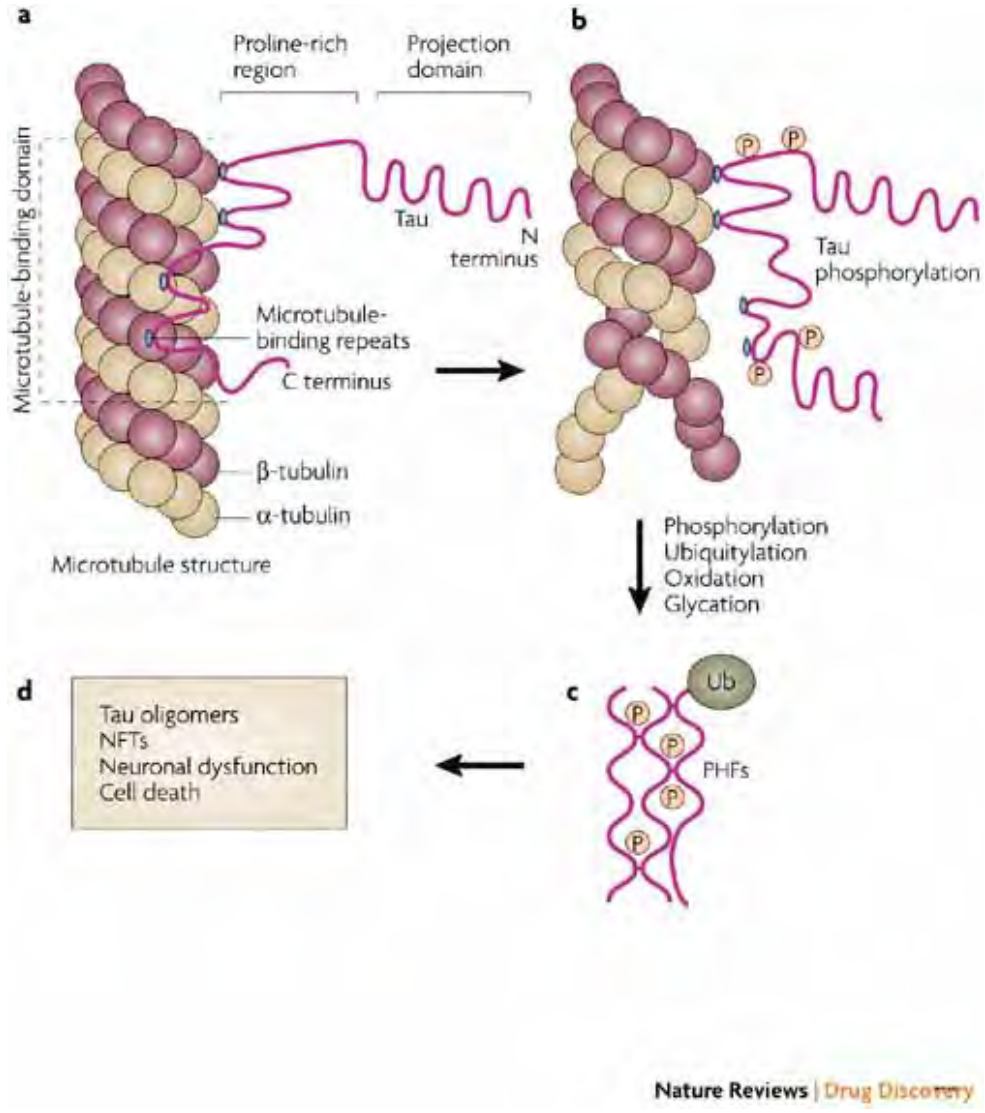

Normal neuron
Vesicles
Tau
Pathological tau aggregates
Diseased neuron

Marx 2007

AD and the Brain



Neurons have an internal support structure partly made up of microtubules. A protein called *tau* helps stabilize microtubules. In AD, *tau* changes, causing microtubules to collapse, and *tau* proteins clump together to form neurofibrillary tangles.



Nature Reviews | Drug Discovery

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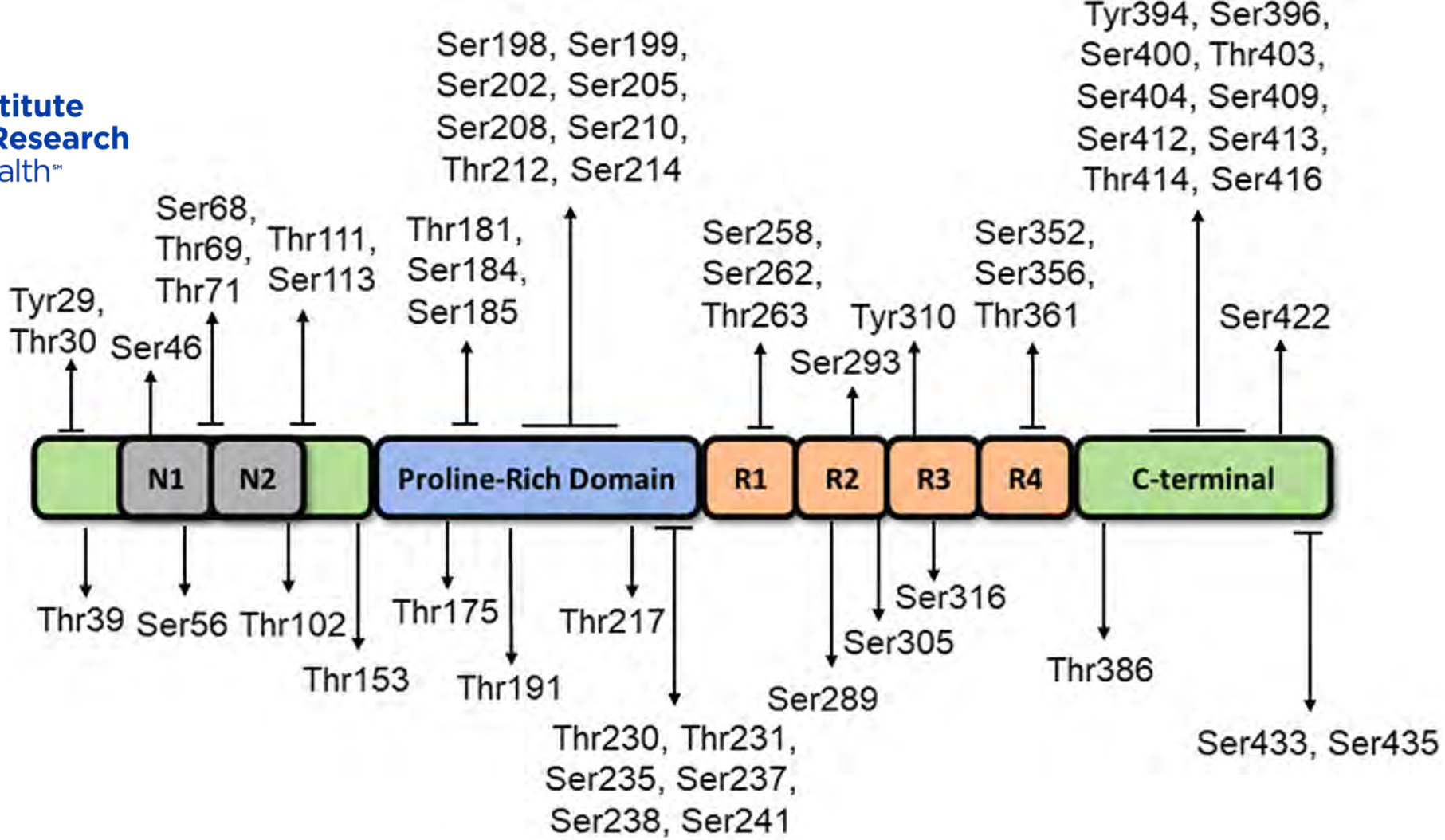
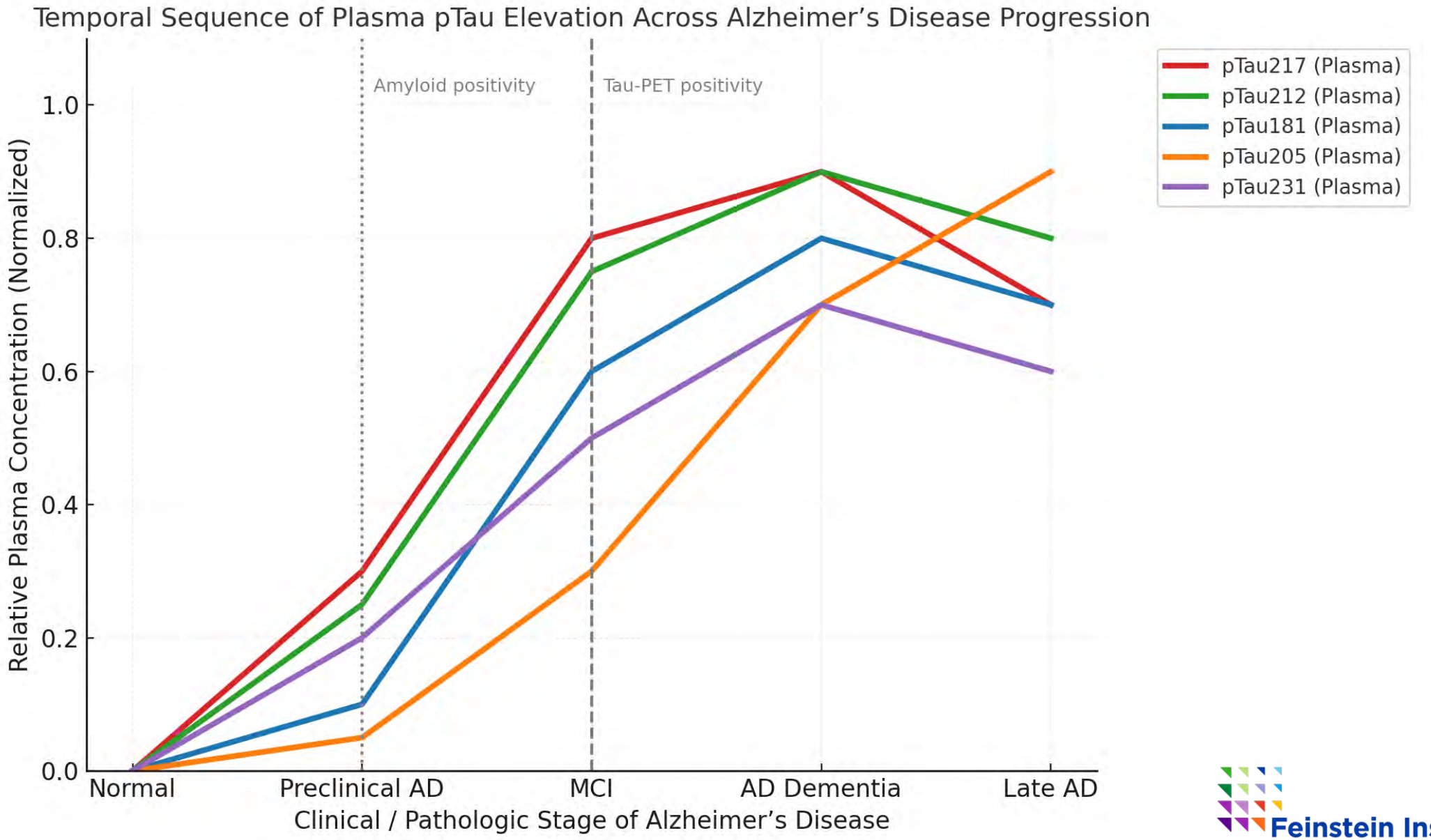


Schematic showing 2N4R tau (441 amino acids), the longest isoform expressed in human brain. Tau protein contains major structural domains including N-terminal domain with N1 and N2 inserts, proline-rich region, four major microtubule-binding repeats (R1–R4), and C-terminal domain. The N1, N2 and R2 regions can be alternatively spliced in the human brain resulting in 6 isoforms: 0N3R, 1N3R, 2N3R, 0N4R, 1N4R, and 2N4R. The position of identified phosphorylation sites found in AD brains are shown. (Xia et al., 2021, Molecular Neurodegeneration)



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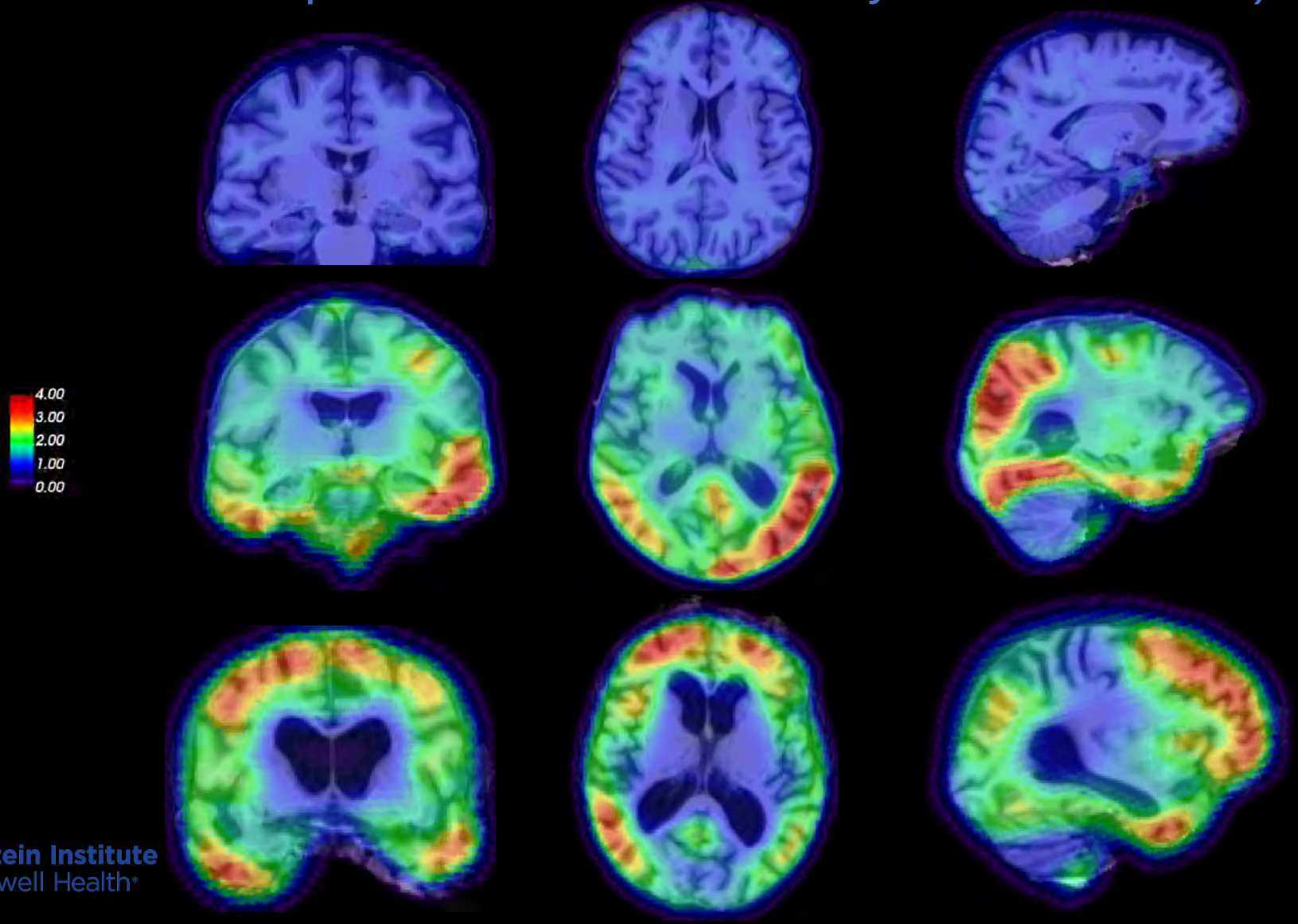
Next generation [^{18}F]-PI2620 tau PET in AD+P (FDA IND): “Tau Networks” (Funded by Alzheimer’s Foundation of America, https://clinicaltrials.gov/study/NCT05847192)



Cognitively Healthy

Alzheimer’s Disease

Alzheimer’s Disease with Psychosis

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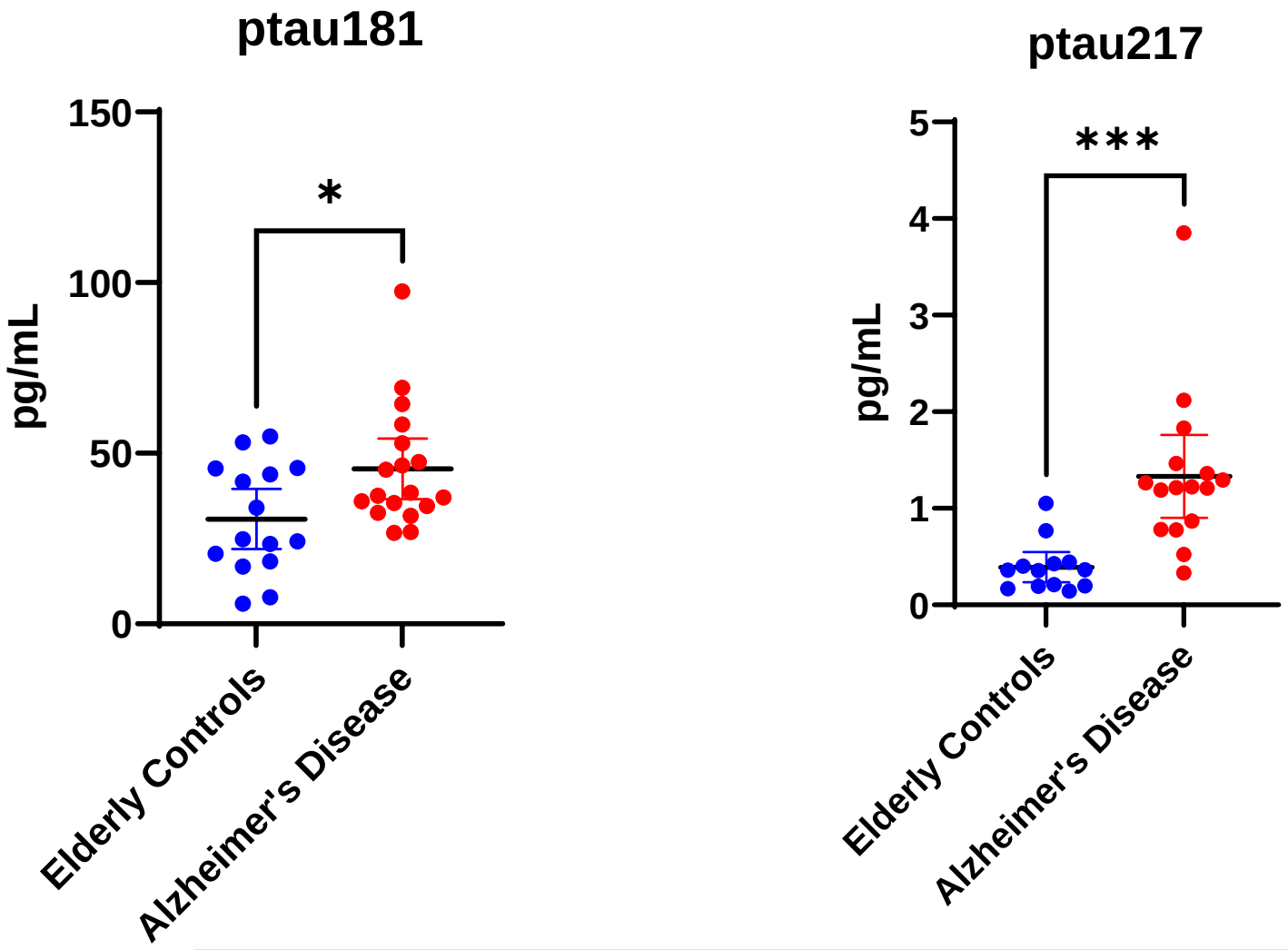
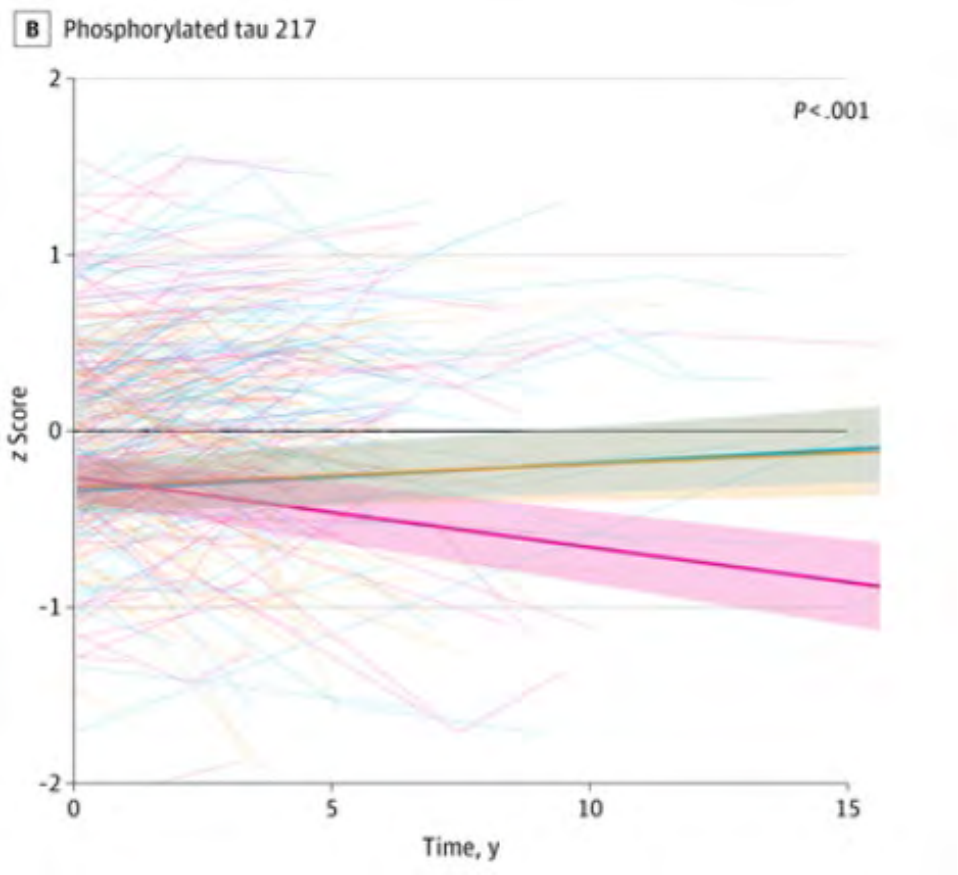


Ptau in PI-2620 LZ Center positive and negative scans

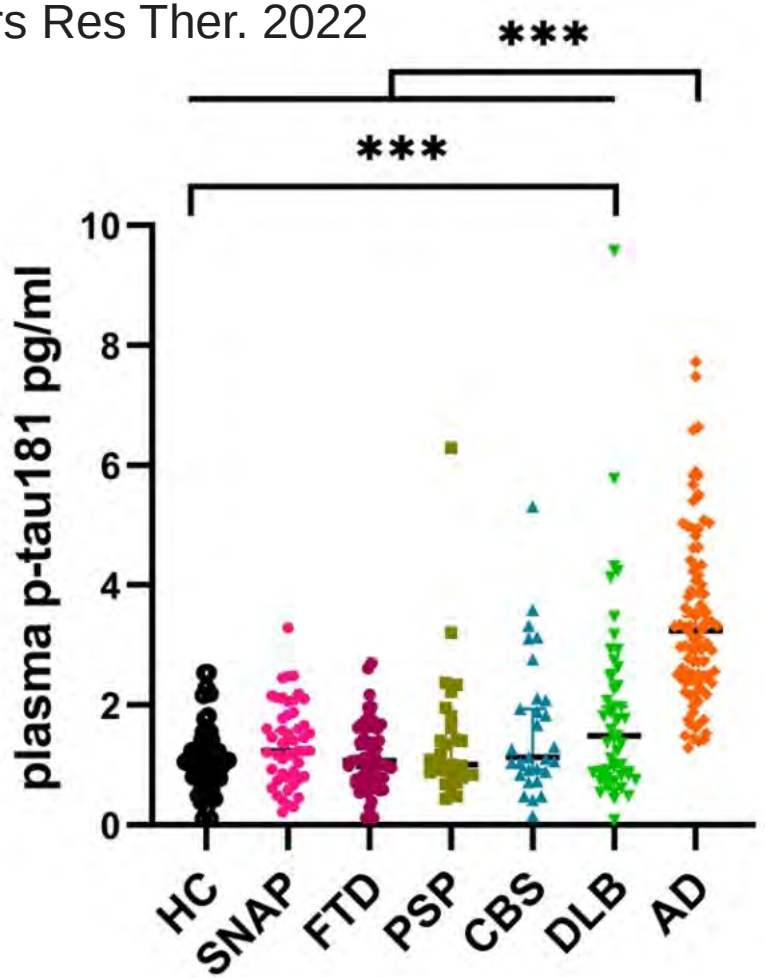
Trieu C, van Harten AC, van Leeuwenstijn MSSA, et al. Longitudinal Blood-Based Biomarkers and Clinical Progression in Subjective Cognitive Decline. *JAMA Netw Open.* 2025;8(12)



A total of 298 individuals (mean [SD] age, 61.55 [8.08] years; 174 [58.4%] male) with no dementia or MCI but subjective cognitive complaint were included, and followed for 15 years (X axis) looking at change in cognition over time (Y)

Steeper pTau217 slope was associated with progression from SCD to mild cognitive impairment or dementia (hazard ratio [HR], 3.6; 95% CI, 1.8-7.4 per 0.05 SD increase per year;

Baiardi S, et al. Diagnostic value of plasma **p-tau181**, NfL, and GFAP in a clinical setting cohort of prevalent neurodegenerative dementias. Alzheimers Res Ther. 2022 Oct 12;14(1):153.



FTD frontotemporal dementia, *PSP* progressive supranuclear palsy, *CBS* corticobasal syndrome, *DLB* dementia with Lewy bodies, *AD* Alzheimer disease, *SNAP* suspected non-AD physiopathology, *HC* healthy controls

Palmqvist S, Janelidze S, Quiroz YT, et al. Discriminative Accuracy of Plasma **Phospho-tau217** for Alzheimer Disease vs Other Neurodegenerative Disorders. *JAMA.* 2020;324(8):772–781

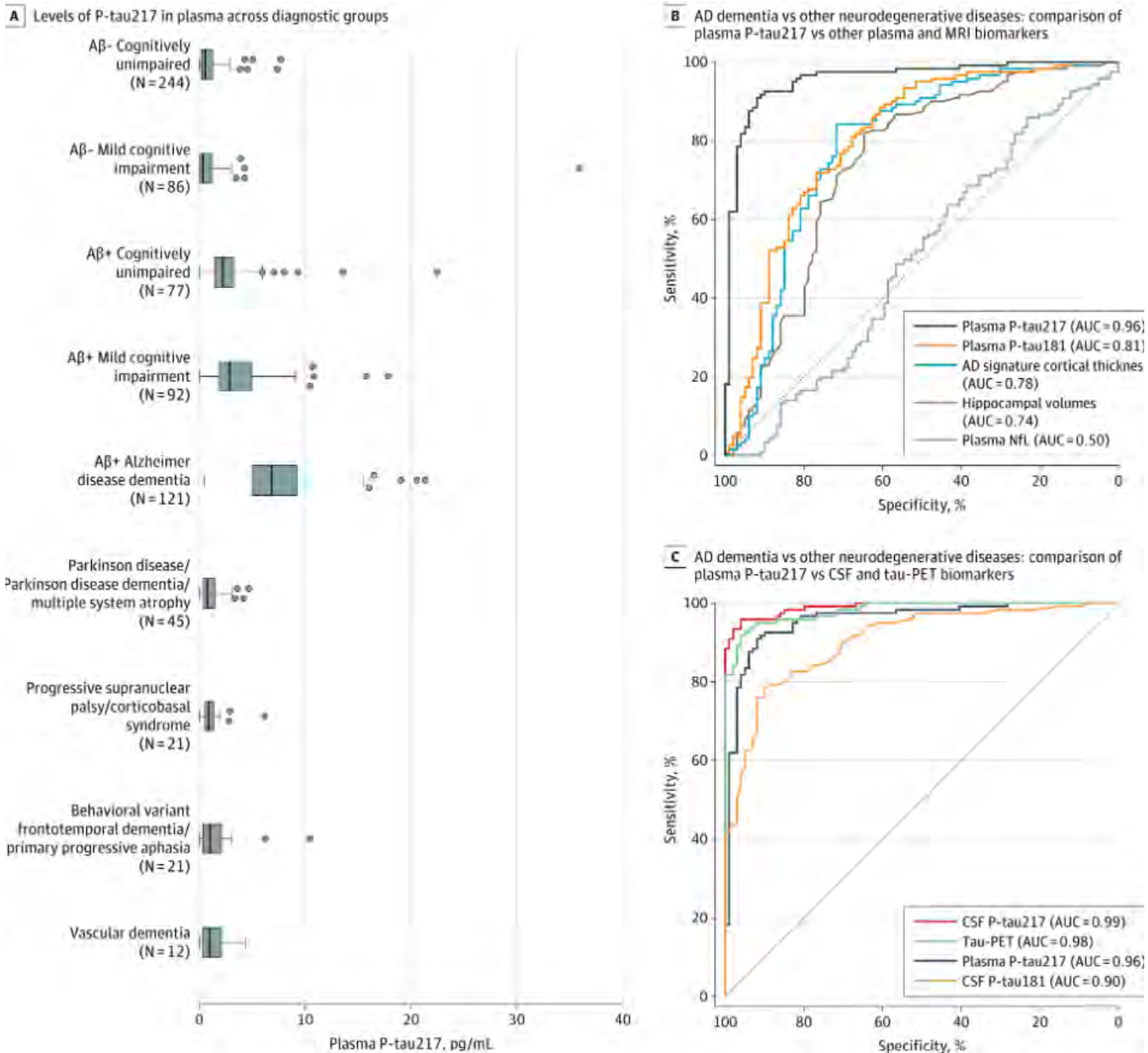


Figure S1. Plasma ptau181 levels at baseline

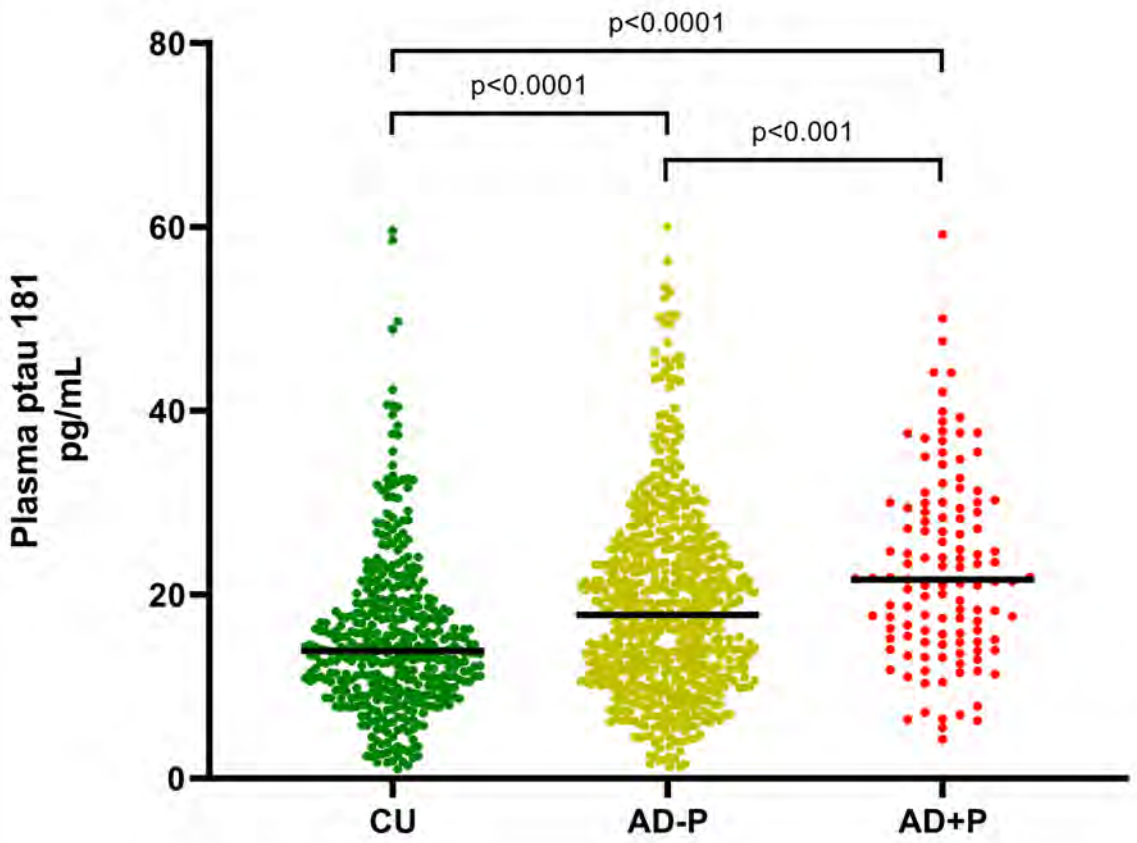
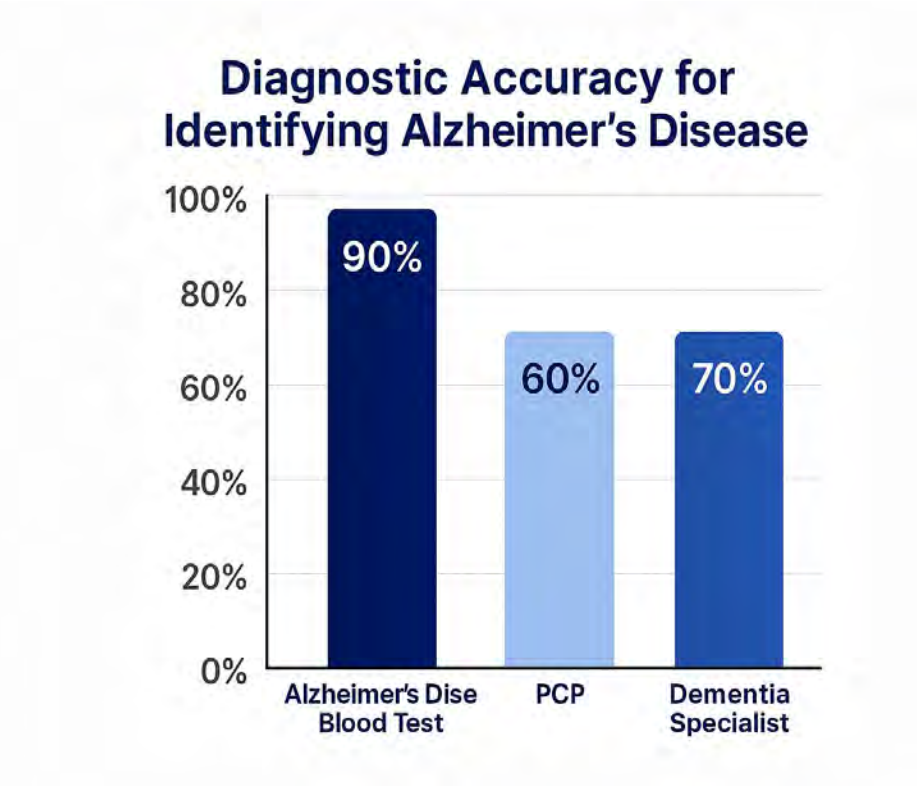


Figure S1. Baseline plasma p-tau181 comparison between groups. CU group showed lower ptau181 values compared to AD groups. AD-P group showed lower ptau181 values compared to AD+P group. Plasma pg/mL values are showed for clinical interpretation purposes. Log transformed values were used in the GLM analysis, adjusted by age, sex, and education. Statistical significance adjusted for multiple comparisons using Bonferroni correction. CU = Cognitively unimpaired; AD-P = Alzheimer's disease without psychosis; AD+P = Alzheimer's disease with psychosis; GLM = Generalized linear model.

Gomar and Koppel
JAMA Psychiatry, 2024

Palmqvist S, Tideman P, Mattsson-Carlgren N, et al. Blood Biomarkers to Detect Alzheimer Disease in Primary Care and Secondary Care. *JAMA.* 2024;332(15):1245–1257.



- How does blinded office plasma ptau217 assay with cutoff values perform against the diagnostic acumen of PCPs and Dementia Specialists in accurately identifying patients with AD pathology and clinical AD??
- Physicians blinded to biomarkers based their diagnosis (does this patient have AD?) on 'standard evaluation' (clinical exam, cognitive testing, imaging)
- AD pathology was determined by amyloid PET, CSF ptau217, and clinical diagnosis according to IWG criteria (Dubois et al., clinical symptoms +biomarker)
- 1213 participants undergoing dementia workup for cognitive complaint in primary and secondary clinics, 50% with confirmed AD pathology (below), age 60s-80s, MMSEs 22-29
- **PCPs had a diagnostic accuracy of 58%(95% CI 51-65), Dementia Specialists 71% (95% CI 67-76) and plasma ptau217 93%(95% CI 90-95)**
- Performed well despite high rate of medical comorbidities including 26% with CKD

Conclusions

- Blood tests including plasma ptau181 and ptau217 that are currently approved by FDA have utility in the differential diagnosis of Alzheimer’s disease and are likely to become more widely utilized in the near future
- These tests should be integrated into a clinical evaluation for those suffering with impairment and not used to predict the future in those who are worried about their risk of developing dementia



For Tau Biomarkers research sponsored by AFA:

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