Workshop 1

The Science and Promise of Blood-Based Biomarkers in Alzheimer's Disease

PeerView Live

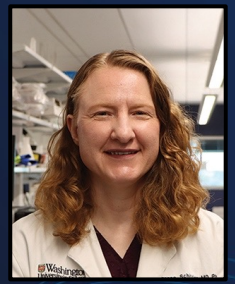
Part 1 of a 3-part workshop series

Goals for Today

During today's workshop, we will learn that…

- Recent advances in blood-based biomarker (BBM) testing have greatly expanded access to minimally invasive and cost-effective tools that support early and accurate diagnosis of Alzheimer's disease (AD)
- BBMs can accurately predict brain amyloid pathology and correlate with cognitive decline and dementia risk in AD

The Importance of Blood-Based Biomarkers in AD Diagnosis



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Let's Start With A Case

	Primary Care Clinician Next Steps
Clinical assessment	• Patient and family interview, medication review, neurological screen, MoCA, and some basic lab work – Self-reported symptoms were corroborated by her husband • MoCA score: 24/30 (with 1 out of 5 on verbal recall) • No impairment in basic or instrumental ADLs • No other remarkable findings
Diagnosis	• Mild cognitive impairment (MCI) • Underlying cause of her symptoms presumed to be AD
Referral	• Referred to neurology so Margaret could undergo biomarker testing to determine whether AD pathology is contributing to her cognitive changes • However, because Margaret lives in an area where the wait list for a neurology appointment is 18 months long and the nearest PET imaging center is 3 hours away, her clinician decided to order blood-based biomarker testing

Benefits of Early Detection and Biomarker-Confirmed Diagnosis of Alzheimer's Disease[1-10]

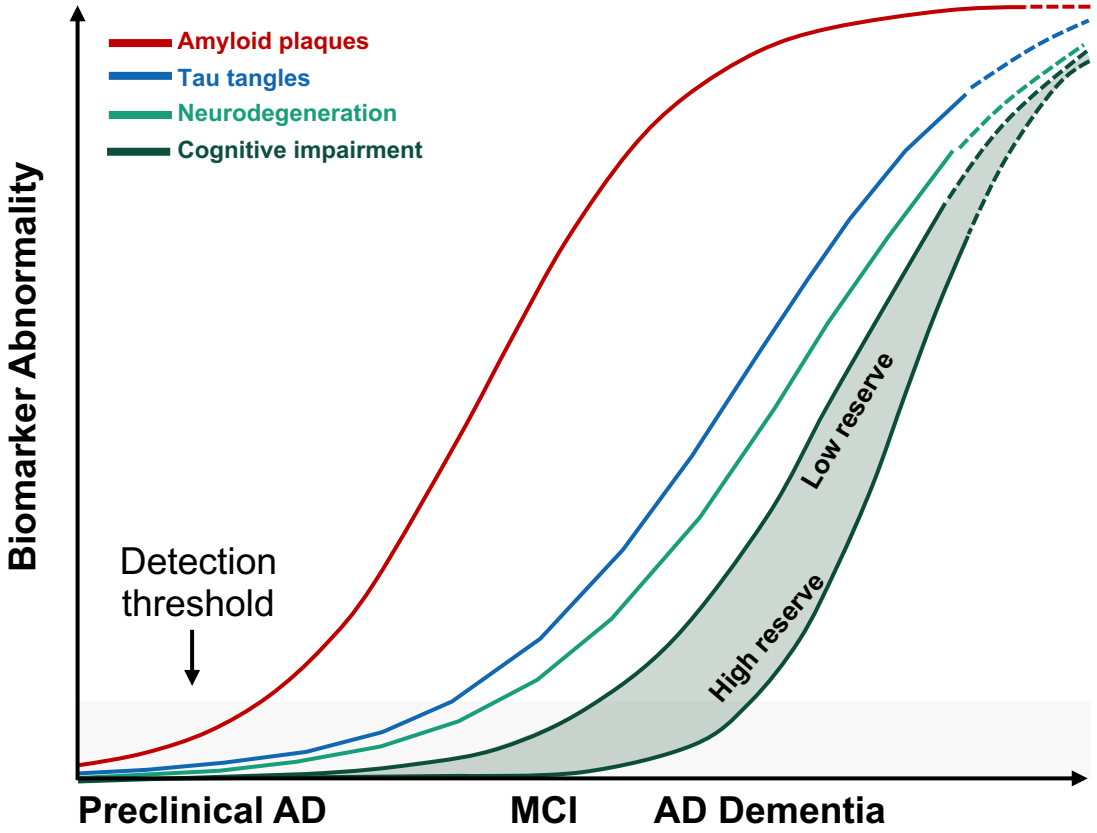
Why is it important for patients experiencing cognitive decline to receive an early and accurate diagnosis?

- Validates patient and family concerns with a specific diagnosis
- Enables patients to participate in their own care planning while they are still capable
- Empowers patients to make lifestyle changes that may slow progression of the disease and manage comorbidities
- Facilitates access to education and personalized support services
- Biomarker confirmation is required for treatment with recently approved disease-modifying therapies for AD
- Clinical trials are available for individuals at early stages of cognitive impairment, including at the prevention stage

1. Sims JR et al. *JAMA*. 2023;330:512-527. 2. Van Dyck CH et al. *N Engl J Med*. 2023;388:9-21. 3. Omura JD et al. *MMWR Morb Mort Wkly Rep*. 2022;71:680-685.
4. https://aspe.hhs.gov/reports/national-plan-2021-update. 5. Li G et al. CTAD 2023. Abstract P145. 6. Liss JL et al. *J Intern Med*. 2021;290:310-334. 7. Porsteinsson AP et al. *J Prev Alzheimers Dis*. 2021;3:371-386. 8. https://www.agreedementia.org. 9. Marasco RA. *Am J Manag Care*. 2020;26:S167-S176.
10. https://www.alz.org/media/Documents/alzheimers-early-detection-diagnosis-ph-fs.pdf.

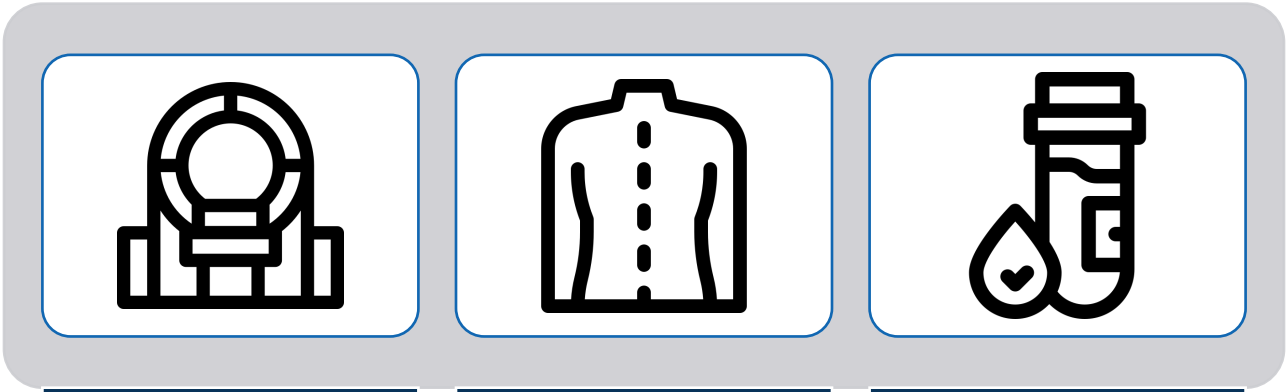
Temporal Evolution of Alzheimer's Disease Pathology and Cognitive Impairment[1]

- Pathological processes start with the development of amyloid (Aβ) plaques, followed by tau tangles, then neurodegeneration
- Biomarker tests are used to determine whether AD pathology is present and may be causing or contributing to cognitive impairment



1. Jack Jr CR et al. *Lancet Neurol.* 2013;12:207-216.

Clinically Available Alzheimer's Disease Biomarker Tests



- PET imaging
- CSF tests
- Blood tests

Clinicians and Patients Need Blood-Based Biomarker Tests in the Era of Disease-Modifying Therapies for AD[1-5]

Full FDA approvals of lecanemab in July 2023 and donanemab in July 2024 greatly increased the need for AD biomarker testing because these therapies require confirmation of amyloid pathology before starting treatment

Benefits of BBMs:

- BBM tests may be the only modality that will enable adequate volumes of testing
- Less invasive, more accessible, and less expensive
- More acceptable than CSF testing or amyloid PET for patients
- Can potentially improve equitable access to new therapies by enabling triage testing in primary care, thereby decreasing wait time for biomarker testing and alleviating burden on healthcare system

1. Mielke M et al. *Alzheimers Dement*. 2024;20:8216-8224. 2. Hansson O et al. *Alzheimers Dement*. 2022;18:2669-2686.
3. Schindler SE et al. *Nat Rev Neurol*. 2024;20:426-439. 4. Pleen J et al. *Pract Neurol*. 2024;23:27-42. 5. Hampel H et al. *Neuron*. 2023;111:2781-2799.

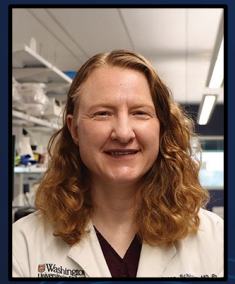
Current Indications for Clinical AD Biomarker Testing[1-5]

- **Clinical AD blood-based biomarker testing is indicated for patients who have undergone a comprehensive diagnostic workup for cognitive impairment** and who have objective evidence of cognitive impairment, and
  - In whom AD is a potential cause of cognitive impairment,
  - AND biomarker testing is expected to affect diagnosis and/or management by
    - Improving the accuracy of an MCI or a dementia diagnosis
    - And/or determining whether patients may be candidates for AD-specific treatments, such as amyloid-targeting therapies (ATTs)
- **Biomarker testing is not currently recommended for individuals who are not cognitively impaired**

1. Johnson KA et al. *Alzheimers Dement*. 2013;9:e106-e109. 2. Shaw LM et al. *Alzheimers Dement*. 2018;14:1505-1521. 3. Palmqvist S et al. *Alzheimers Dement*. 2025;21:e70535. 4. Cummings J et al. *J Prev Alzheimers Dis*. 2023;10:362-377. 5. Rabinovici GD et al. *J Prev Alzheimers Dis*. 2025;12:100150.

The Science Behind the Promise

Evaluating the Evidence for BBMs in AD



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Clinically Available Blood Tests in the United States

Company	Test Name	Assay Type	Biomarkers	Website
C2N Diagnostics	PrecivityAD; PrecivityAD2	IP-MS	Aβ42/40, age, *APOE* proteotype; Aβ42/40, %p-tau217	precivityad.com
Labcorp	Fujirebio Lumipulse	Immunoassay	P-tau217, Aβ42/40, **p-tau181,[a] p-tau217/Aβ42[a]**	labcorp.com/treatment-areas/neurology/conditions/neurodegenerative/alzheimers
Mayo Clinic Laboratories	Phospho-Tau217	Immunoassay	P-tau217	news.mayocliniclabs.com/neurology/alzheimers-disease
Roche	pT181p Elecsys E2G 100	Immunoassay	P-tau181[a]	diagnostics.roche.com/us/en/products/lab/elecsys-phospho-tau-181p-plasma-pid00001042.html#specs
Quanterix	ALZpathDx Janssen LucentAD	Simoa	P-tau217	alzpath.bio/clinicians lucentdiagnostics.com/providers
Quest Diagnostics	AD-Detect	IP-MS for Aβ42/40; immunoassay for p-tau217 and p-tau181	Aβ42/40, p-tau217, p-tau181, **p-tau181,[a] p-tau217/Aβ42[a]**	questdiagnostics.com/healthcare-professionals/about-our-tests/neurological-disorders/campaigns/alzheimers-risk-assessment

[a] FDA cleared.

What Do Different Blood Biomarkers Represent?[1]

Amyloid-Tau- Neurodegeneration (ATN) Profile

Labcorp is the first company to make a fully blood-based ATN Profile commercially available - giving physicians a simple, objective test for Alzheimer's disease pathology that can help shorten the time to diagnosis.

What is ATN?

The ATN framework establishes a means for classifying biomarkers based on the biological evidence of Alzheimer's disease that each marker provides1. These markers are divided into three categories to reflect the three primary biological changes associated with Alzheimer's:

- **A for amyloid plaques:** Accumulations of beta-amyloid 42 proteins begin to form plaques in the brain years before initial symptom onset
- **T for tau tangles:** The beta-amyloid 42 accumulation causes misfolding of tau proteins, which tangle into knots and disrupt normal brain cell function
- **N for neurodegeneration:** Brain cell functional impairment causes the cells to die, which exacerbates the characteristic cognitive impairment symptoms observed in Alzheimer's patients

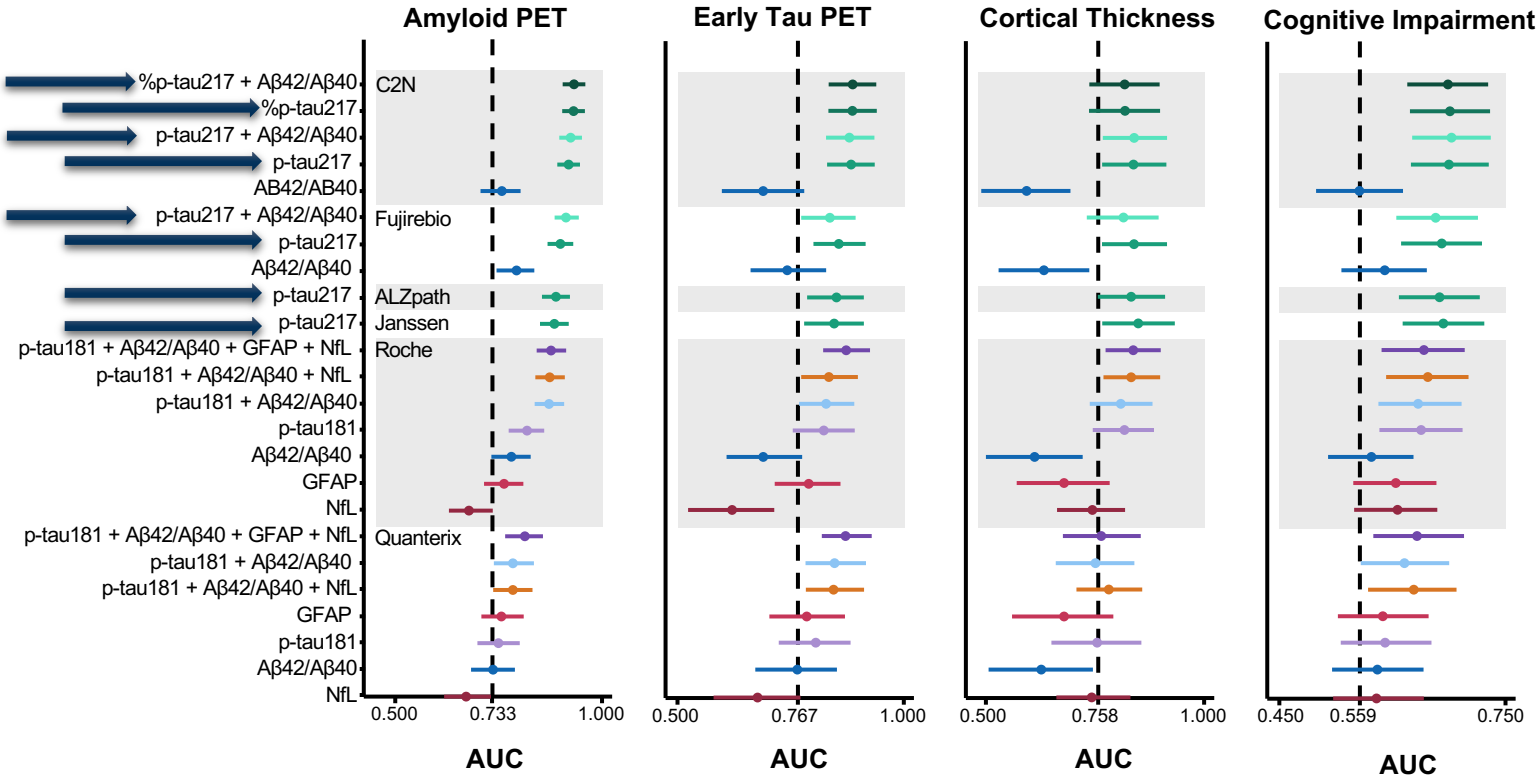
Category		
A	Beta-Amyloid 42/40 Ratio	Assess levels of pathologic change consistent with Alzheimer's disease
T	Phosphorylated Tau 181 (pTau181)	
N	Neurofilament Light Chain (NfL)	Assess disease severity by measuring neurodegeneration

1. https://www.labcorp.com/tests/484400/atn-profile.

Is This Plasma ATN Framework Correct?

- Hypothesis: Plasma Aβ42/40 is most strongly associated with amyloid pathology
- Hypothesis: Plasma p-tau181 is most strongly associated with tau pathology
- Hypothesis: Plasma NfL is most strongly associated with cortical thickness and cognitive impairment
- Hypothesis: The combination of multiple biomarkers is better than one biomarker

Plasma P-Tau217 Tests Are the Best Predictors of Biological and Clinical Markers of AD[1]



FNIH
Foundation for the National Institutes of Health

BIOMARKERS CONSORTIUM
IMPROVING HEALTH THROUGH MEANINGFUL MEASUREMENTS

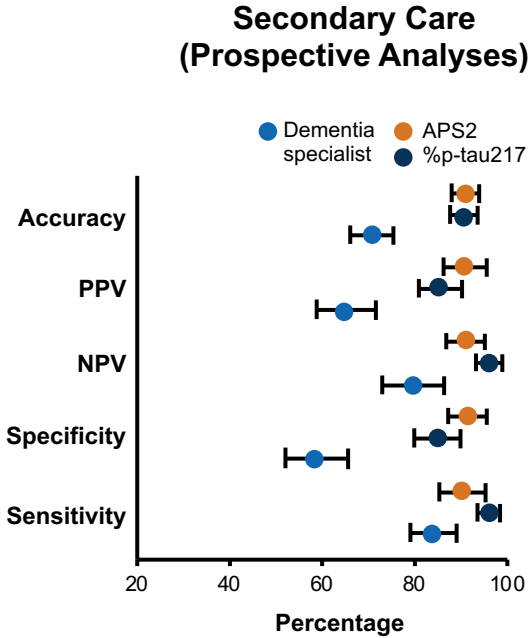
ADNI
Alzheimer's Disease Neuroimaging Initiative

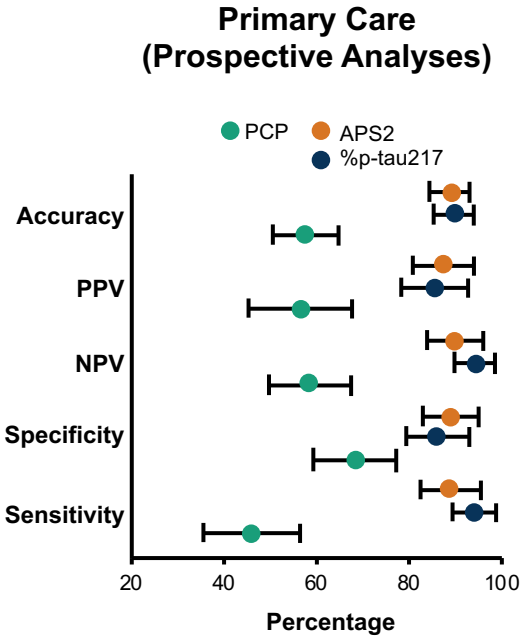
Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

1. Schindler SE et al. *Alzheimers Dement.* 2024;20:8074-8096.

Plasma %P-Tau217 With and Without Aβ42/Aβ40 Is Highly Accurate[1]

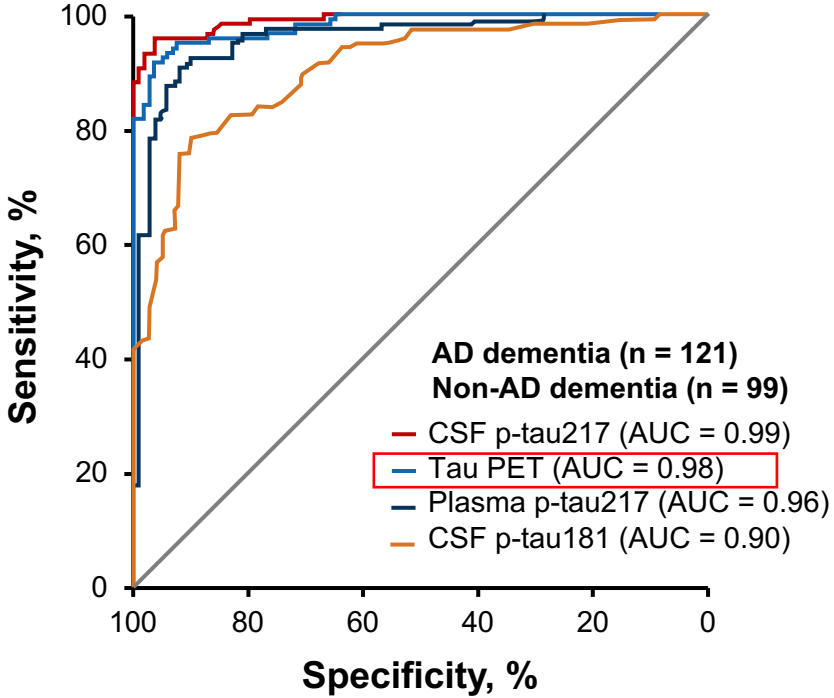
- Plasma %p-tau217 combined with Aβ42/Aβ40 plasma ratio (APS2) improved diagnostic accuracy in both primary and secondary care
  - Clinical diagnosis is incorrect ~40% of the time in primary care and ~25% of the time in specialty care
  - Biomarker testing increased the diagnostic accuracy to >90% in both care settings





1. Palmqvist S et al. *JAMA*. 2024;332:1245-1257.

Plasma P-Tau217 Differentiates as Well as CSF and PET Among AD and Other Types of Dementia[1]



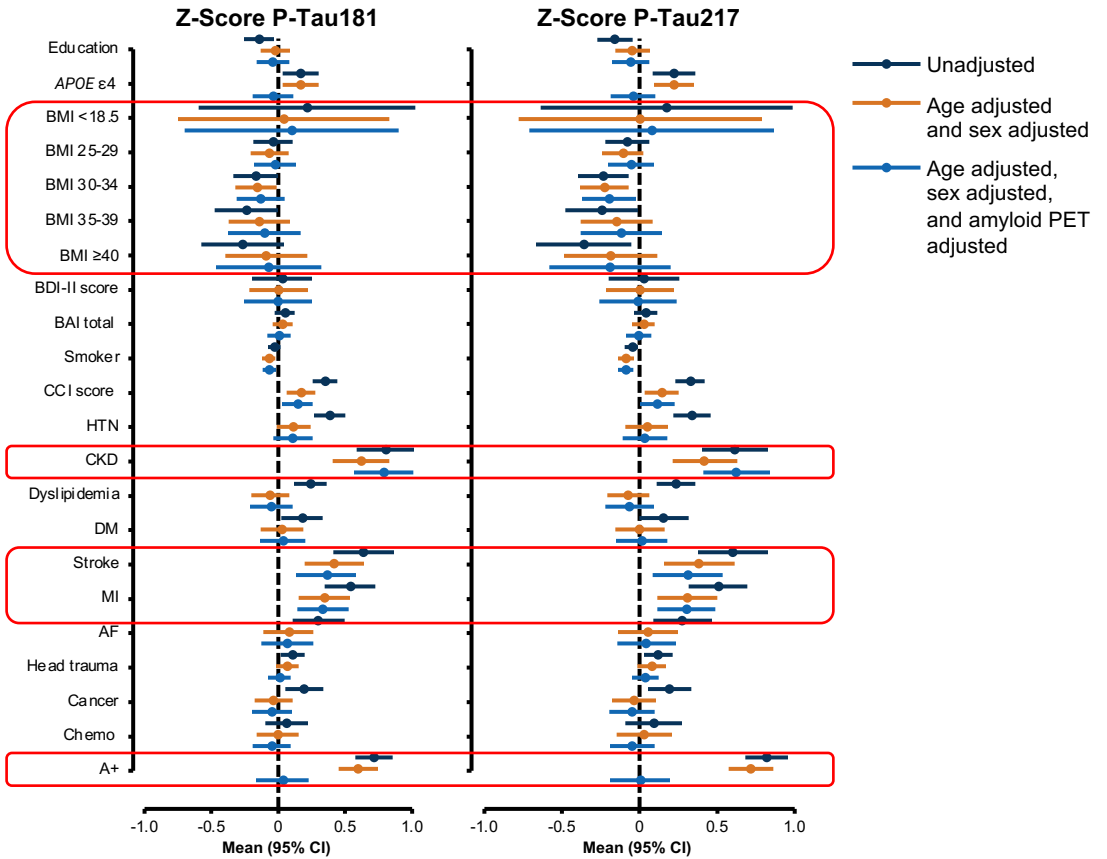
- Plasma p-tau217 can differentiate AD dementia from non-AD dementia at rates similar to CSF p-tau217 and tau PET
- However, even in patients who are amyloid positive, AD may not be the driving force behind cognitive decline
  - AD can be comorbid with another condition that is contributing to cognitive decline (ie, mixed pathology)
- Almost all older patients are amyloid positive; therefore, AD biomarker tests are more useful when they are negative in elderly patients

1. Palmqvist S et al. *JAMA*. 2020;324:772-781.

Interpreting Blood-Based Biomarkers

Understanding the Effect of Comorbidities on Plasma P-Tau181 and P-Tau217 Levels[1-5]

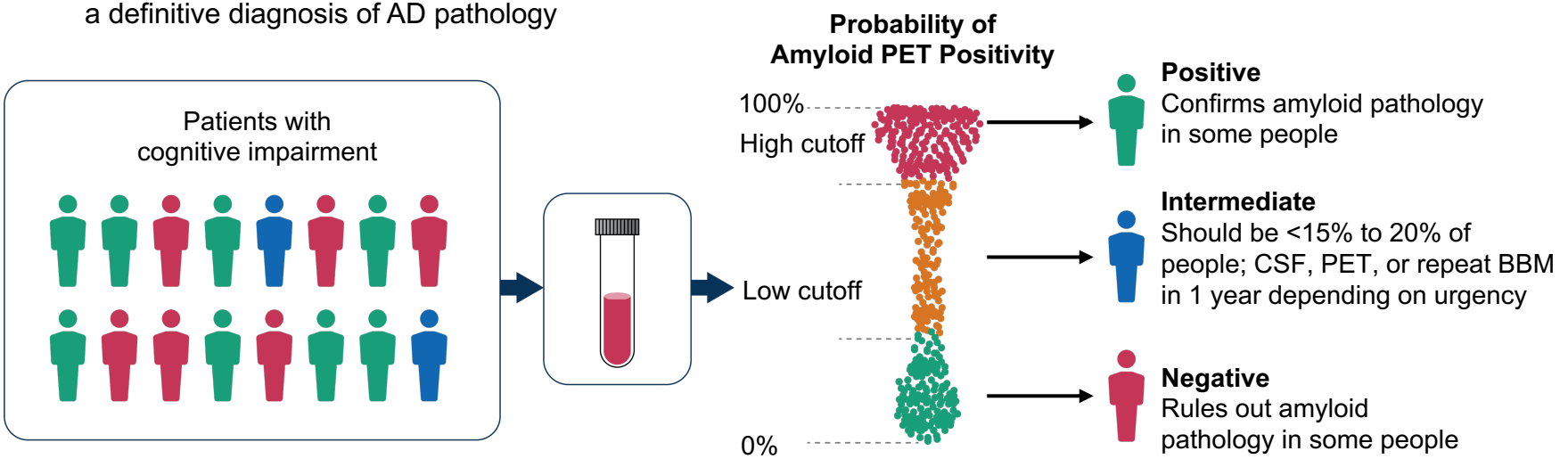
- **Chronic kidney disease (CKD),** BMI, smoking, stroke, and myocardial infarction affect plasma p-tau181 and p-tau217 levels, even after adjusting for age, sex, and amyloid PET findings
- AD blood tests are most affected in patients with severe CKD (EGFR <45)
- For this reason, renal function should be measured at the same time as blood-based biomarker testing



1. Mielke MM et al. *Nat Med*. 2022;28:1398-1405. 2. Bornhorst JA et al. *Neurology*. 2025;104:e210287. 3. Schöll M et al. *Lancet Healthy Longev*. 2024;5:100630. 4. Arslan B et al. *Alz Res Therapy*. 2025;17:48. 5. Piura YD et al. *Alzheimers Dement*. 2025;21:e70316.

Two-Cutoff Approach for BBM Tests for Amyloid Pathology[1,2]

- Use of two cutoff values for BBM testing in people with cognitive symptoms leads to three categories of results, increasing the accuracy with which people can be classified as having/not having amyloid pathology
- Interpretation of positive and negative results depends on the clinical suspicion of AD
  - **Positive test** indicates a higher risk for having amyloid plaques in those with a higher suspicion of AD pathology but may not provide a definitive diagnosis of AD pathology
  - **Negative test** is likely to rule out AD pathology in patients with a lower suspicion of AD pathology but may not provide a definitive diagnosis of AD pathology

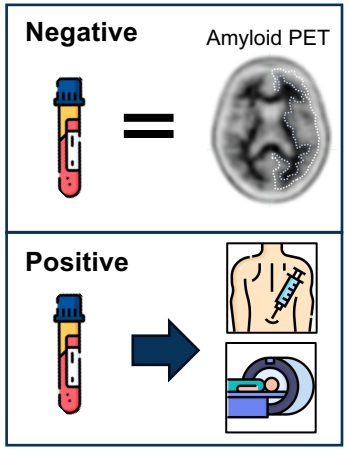


1. Schindler SE et al. *Nat Rev Neurol*. 2024;20:426-439.
2. https://static1.squarespace.com/static/65957483277c0a184f111f09/t/65f1bc429eb1871aa84bdff1/1710341187541/Flyer+5.pdf.

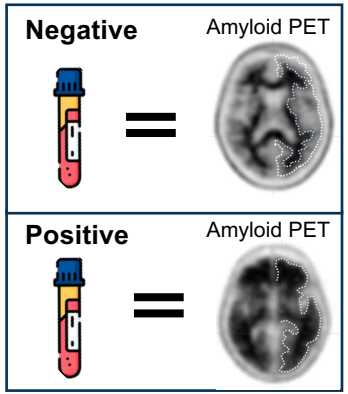
Two Uses of BBM Tests: Triaging and Confirmation[1]

Download the Practice Aid!

- **Triaging:** BBM tests with ≥90% sensitivity and ≥75% specificity can be used as triaging tests
  - A **negative test** identifies individuals who are unlikely to have amyloid pathology—no further testing for AD is necessary
  - A **positive test** identifies individuals with a higher likelihood of amyloid pathology who need a second test to confirm the presence of amyloid pathology—perform further testing with CSF or PET



- **Confirmation:** BBM tests with ≥90% sensitivity and specificity can serve as confirmatory tests
  - A **negative test** identifies individuals who are unlikely to have amyloid pathology—no further testing for AD is necessary
  - A **positive test** identifies individuals who are likely to have amyloid pathology



1. Palmqvist S et al. *Alzheimers Dement*. 2025;21:e70535.

Biomarker Results Must Be Interpreted in the Context of Patients' Clinical Symptoms and Pretest Probabilities[1,2]

- BBM tests should not be obtained before a comprehensive clinical evaluation, and test results should always be interpreted within the clinical context
- Consider the **pretest probability of AD pathology** for each patient when interpreting BBM tests
  - The **positive** and **negative predictive values** depend on the likelihood of AD pathology before testing

Patient Presentation	Pretest Probability of Amyloid Pathology, %	Positive BBM Result	Negative BBM Result
75-year-old patient with a typical AD dementia syndrome	85	98% of patients have a true-positive result (have amyloid pathology)	61% of patients have a true-negative result (do not have amyloid pathology)
		2% of patients have a false-positive result (do not have amyloid pathology)	39% of patients have a false-negative result (have amyloid pathology)
60-year-old patient with subjective cognitive decline	20	69% of patients have a true-positive result (have amyloid pathology)	97% of patients have a true-negative result (do not have amyloid pathology)
		31% of patients have a false-positive result (do not have amyloid pathology)	3% of patients have a false-negative result (have amyloid pathology)

The AD biomarker test is assumed to have 90% sensitivity and specificity for amyloid pathology

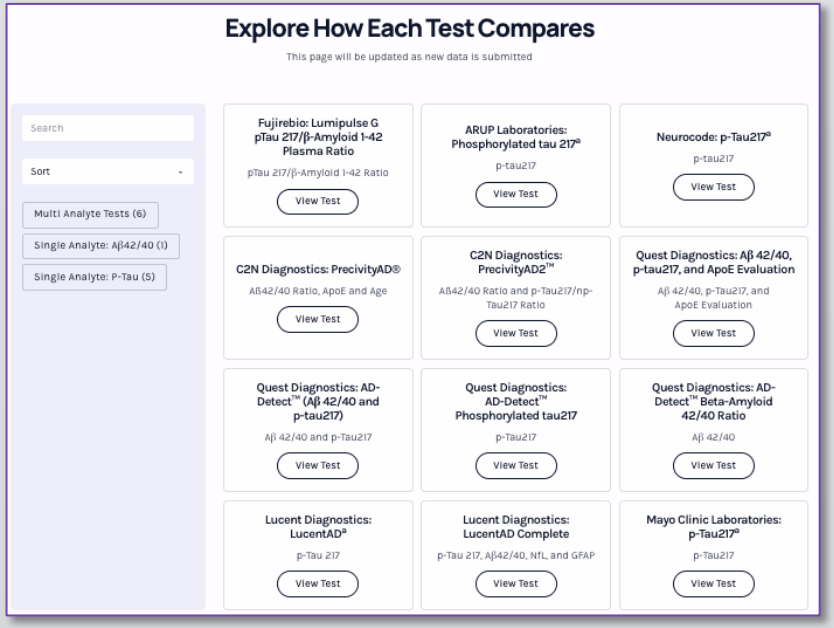
1. VandeVrede L, Schindler SE. *Alzheimers Dement*. 2025;21:e14201. 2. Therriault J et al. *Nature Aging*. 2024;4:1529-1537.

Practice Aid: Tools to Facilitate the Clinical Implementation of Blood-Based Biomarkers for AD

The **Alzheimer's Disease Blood Test Performance Database** and the **Alzheimer's Disease Blood Test PPV/NPV Calculator** provide valuable information about the performance of blood-based biomarkers that are currently on the market

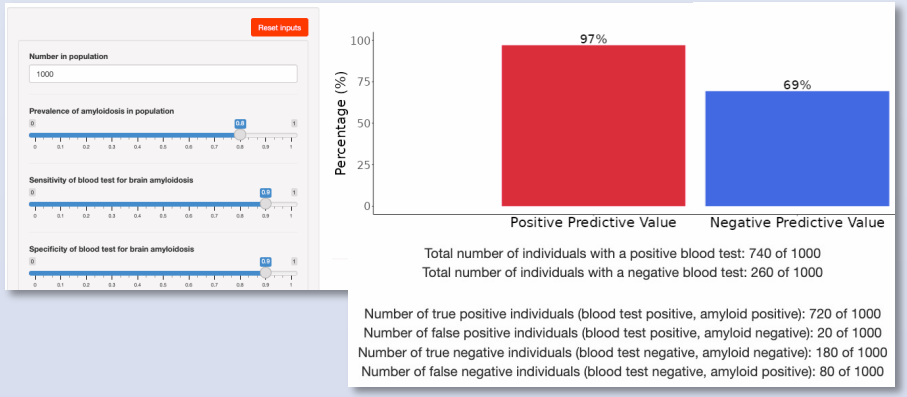
Alzheimer's Disease Blood Test Performance Database

https://alzdiagnostichub.org/blood-test-performance-database/



Alzheimer's Disease Blood Test PPV/NPV Calculator

https://amyloid.shinyapps.io/NPV_PPV/



Download the Practice Aid!

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Take-Home Messages

BBMs are ready for prime time in primary and specialty care settings

- Two FDA-cleared blood tests, with several more on the way
- **P-tau217** tests, alone or in combination, are the most accurate BBMs
- Multiple blood tests based on p-tau217 with accuracy similar to CSF tests are clinically available

Proper implementation of BBMs requires an understanding of what they can and cannot do

- BBMs cannot confirm that AD is the cause of a patient's cognitive decline, particularly in patients with copathologies (eg, cerebrovascular disease, α-synuclein) or in patients with an atypical clinical presentation

It's important that clinicians only order BBM test for patients as part of a cognitive workup and always interpret results in conjunction with other patient clinical information, including the patient's pretest probability

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Join Us for Parts 2 and 3 of the Biomarkers Workshop Series

New Developments Shaping Blood-Based Biomarker Use in Alzheimer's Disease

Live Virtual Workshop Part 2
on Tuesday, January 20, 2026,
7:00-7:30 PM EST

Putting Blood-Based Biomarkers to Work in Real-World Alzheimer's Disease Care

Live Virtual Workshop Part 3
on Thursday, January 29, 2026,
7:00-7:30 PM EST

Featuring:
Hamid R. Okhravi, MD
Shirley and Richard Roberts
Comprehensive Memory Center
Lawrence J. Goldrich Institute for
Integrated NeuroHealth
Eastern Virginia Medical School at
Old Dominion University
Norfolk, Virginia

Featuring:
Lawren VandeVrede, MD, PhD
Weill Institute of Neuroscience
University of California, San Francisco
San Francisco, California

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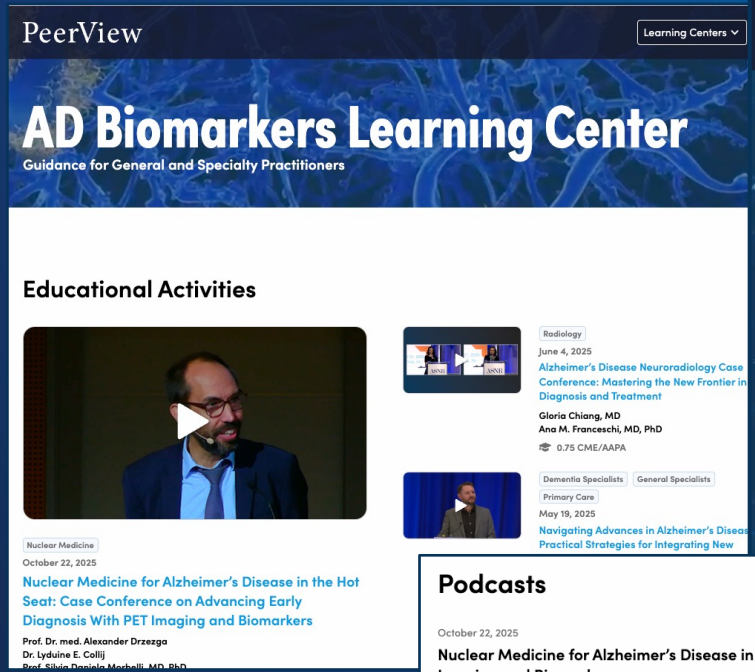

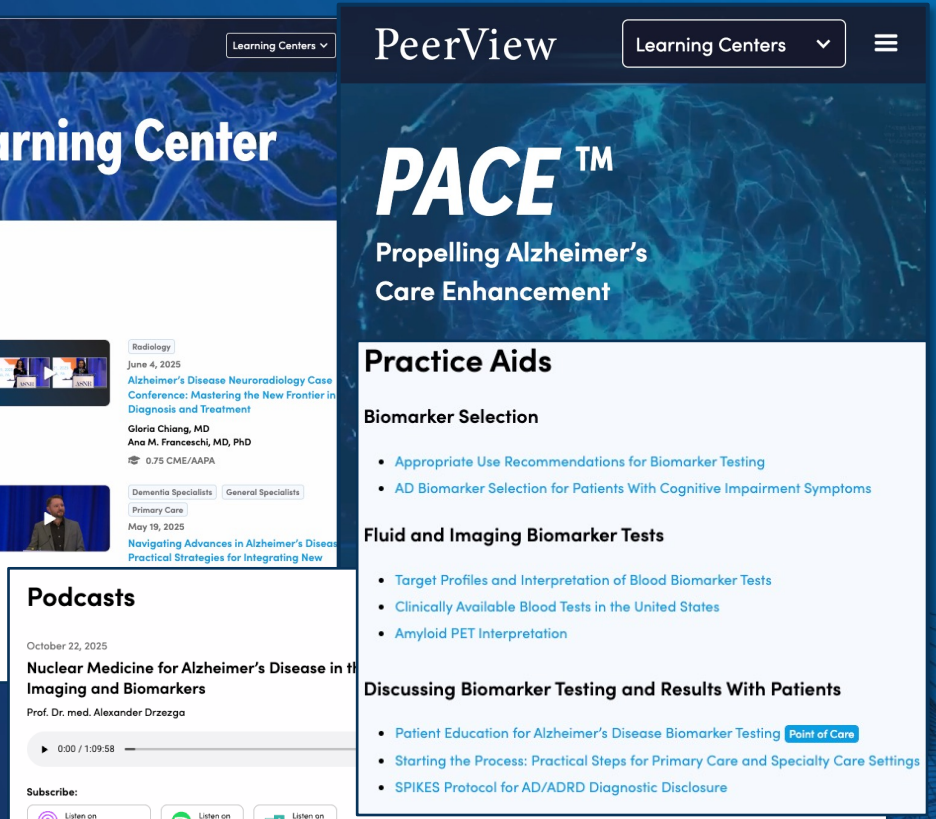

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Abbreviations

- AD: Alzheimer’s disease
- APS2: amyloid probability score 2
- ATN: amyloid-tau-neurodegeneration
- ATT: amyloid-targeting therapy
- Aβ: amyloid-beta peptide
- BBM: blood-based biomarker
- CKD: chronic kidney disease
- CLIA: Clinical Laboratory Improvement Amendments
- CTAD: Clinical Trials on Alzheimer's Disease
- MCI: mild cognitive impairment
- MoCA: Montreal Cognitive Assessment
- NfL: neurofilament light chain
- NPV: negative predictive value
- P-Tau181: phosphorylated tau at threonine 181
- P-Tau217: phosphorylated tau at threonine 217
- PPV: positive predictive value