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FROM THE ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE 2024
ALZHEIMER'S DISEASE BLOOD TESTS COULD IMPROVE DIAGNOSIS IN PRIMARY CARE, SPEED RECRUITING FOR RESEARCH & REDUCE WAIT TIMES

Key Takeaways
- **Blood tests that accurately and reliably detect Alzheimer's hallmark brain changes signal a shift to simpler, more accurate and earlier detection and diagnosis, potentially superseding current methods that are expensive, invasive and not always accessible.**
- **A blood test was around 90% accurate in identifying Alzheimer's disease in patients with cognitive symptoms seen in primary care and at specialized memory care clinics. In the research study, primary care physicians were 63% accurate and specialists were 73% accurate when not using the blood test.**
- **Blood tests, once they are confirmed, could enhance recruitment for Alzheimer's clinical trials and slash wait times for Alzheimer's disease assessment.**

PHILADELPHIA, July 28, 2024 — As highly accurate blood tests for Alzheimer's disease are moving closer to use in physician's offices, new research suggests that they may revolutionize the accuracy of diagnosis and provide a cleaner, quicker path to research participation and treatment, according to data reported today at the Alzheimer's Association International Conference® (AAIC®) 2024, in Philadelphia and online.

Dementia is often underdiagnosed—and if it is diagnosed by a clinician, many people nonetheless are unaware or uninformed of their diagnosis, according to the *2024 Alzheimer's Disease Facts and Figures* report. Blood tests for Alzheimer's are demonstrating in research that they could significantly improve a clinician's accuracy and confidence, provide greater accessibility and a platform for enhanced communication.

Blood tests that show the most promise for identifying Alzheimer's-related changes in the brain assess phosphorylated tau (p-tau) protein, an Alzheimer's biomarker that can build up before patients show signs of cognitive impairment. Increases in the specific marker p-tau217 over time correlate with worsening cognition and brain atrophy. The p-tau217 test also predicts the likelihood of amyloid plaques in the brain, which are another biomarker for Alzheimer's and the target for recently approved treatments.

"Blood tests, once they (a) are confirmed in large populations to be more than 90% accurate and (b) become more widely available, show promise for improving, and possibly redefining, the clinical trial recruitment process and the diagnostic work-up for Alzheimer's," said Maria C. Carrillo, Ph.D., Alzheimer's Association chief science officer and medical affairs lead. "While at this time doctors in primary and secondary care should use a combination of cognitive and blood or other biomarker testing to diagnose Alzheimer's, blood tests have the potential to increase the accuracy of early diagnoses and maximize the opportunity to access Alzheimer's treatments as early as possible for better outcomes."

When considering use of a blood test, the *Alzheimer's Association Appropriate Use Recommendations for Blood Biomarkers in Alzheimer's Disease* should be carefully followed. To help guide health care professionals in incorporating blood tests for Alzheimer's in their clinical practice, the Association has convened a panel of clinical and subject-matter experts and is leading the preparation of clinical practice guidelines for the use of blood biomarkers in Alzheimer's, which will be previewed at AAIC 2024.

Blood Test Can Improve Diagnosis Among Primary Care and Alzheimer's Disease Specialists
A large study, reported for the first time at AAIC 2024, shows that blood tests can do a better job of accurately detecting Alzheimer's than both primary care doctors and specialists who were using traditional diagnostic methods.

In the study, 1,213 patients were tested with the PrecivityAD2 test (known as "APS2"). It uses a combination of (1) plasma phosphorylated-tau217 to not-phosphorylated-tau217 ratio (known as %p-tau217) and (2) the ratio of two types of amyloid ($A\beta42/A\beta40$), and it significantly outperformed clinicians in this study.
- Among 698 patients seen at memory clinics, APS2 was around 90% accurate at identifying Alzheimer's disease while specialists were 73% accurate.
- Among 515 patients seen in primary care, APS2 was also around 90% accurate; primary care physicians were 63% accurate at identifying Alzheimer's.

Researchers observed that the APS2 test was highly accurate even in patients with comorbidities, such as kidney disease, which are common in older patients seen by primary care physicians.

"Notably, these were the results of blood samples that have been shipped bi-weekly for analysis from primary care units, which is similar to routine clinical practice," said lead author Sebastian Palmqvist, M.D., Ph.D., at Lund University, Lund, Sweden. "These results were especially impressive considering that older populations in primary care often have medical conditions that can influence or vary the concentrations of p-tau217."

"We see this as a major step towards global clinical implementation of an Alzheimer's blood test," said senior author Oskar Hansson, M.D., Ph.D., also at Lund University. "It highlights the need for Alzheimer's biomarkers in making a correct diagnosis more of the time. The next steps include establishing clear guidelines for how an Alzheimer's blood test can be used in clinical practice, preferably by implementing these tests first in specialist care and then in primary care. This work is currently ongoing."

The research reported at AAIC is funded in part by the Alzheimer's Association, and is simultaneously published in the *Journal of the American Medical Association*.

Research Shows Blood Tests Could Identify Cognitively Unimpaired People for Clinical Trials
Including people at earlier stages of Alzheimer's in clinical trials could potentially help identify treatments that may be effective when symptoms are mild or absent. A study reported at AAIC 2024 found that p-tau217 blood tests could provide a simple and accurate selection tool for identifying cognitively unimpaired patients who likely have amyloid-beta plaques in their brains.

The researchers analyzed samples from 2,718 cognitively unimpaired participants across 10 different studies who had available plasma p-tau217 and amyloid-beta PET imaging or CSF samples. They found that plasma p-tau217 can positively predict (with a range of 79-86%) the likelihood that a cognitively unimpaired person would also test positive for amyloid-beta pathology on an amyloid PET scan or CSF biomarker. Adding the results from the amyloid-beta CSF test or an amyloid beta PET scan to the analysis after a positive blood sample improves the positive prediction to 90% or above, and thereby confidence in the presence of amyloid in the brain using a plasma p-tau217 test.

"If these numbers hold up and are replicated and confirmed by other independent labs, this approach may reduce the need for lumbar punctures and PET scans for Alzheimer's diagnosis by 80 or even 90 percent," said Gemma Salvadó, Ph.D., lead author of the study and an associate researcher at Lund University. "Our results support that plasma p-tau217 positivity alone may be sufficient as a selection of cognitively unimpaired, amyloid-positive participants for many clinical trials."

Blood Tests Could Drastically Reduce Wait Times for Alzheimer's Diagnosis and Treatment
Approved Alzheimer's treatments are indicated for people with mild cognitive impairment due to Alzheimer's or mild Alzheimer's dementia, and they must have confirmed amyloid-beta biology in the brain. Therefore, it's important to identify people who might benefit as early in the course of the disease as possible. Right now, there are often lengthy wait times to complete comprehensive testing for an Alzheimer's diagnosis due to the limited number of Alzheimer's specialists, and variable and often inequitable access to PET imaging or the expertise required for CSF analysis.

Research reported at AAIC 2024 suggests that using high-performing blood tests in primary care could identify potential Alzheimer's patients much earlier so specialists can determine if they are eligible for new treatments.

The researchers used a well-established forecasting model to predict wait times for people eligible for treatment, accounting for both the limited number of Alzheimer's disease specialists and the growing older population. The model included the projected U.S. population of people 55 and older from 2023 to 2032 and compared two scenarios. The first was that primary care clinicians would decide whether or not to refer a patient to an Alzheimer's disease specialist based on the results of a brief cognitive test. The second was that they would also factor in the results of a high-performance blood test and assume that a blood test would be given to individuals testing positive for early-stage cognitive impairment in primary care and referrals to specialty care would be informed by the test results.

The model suggests that by 2033, people will wait an average of nearly six years (70 months) to understand if they could be eligible for new Alzheimer's treatments if their primary care doctor only used brief cognitive assessments to make referrals. If blood tests were used to rule out Alzheimer's, the average wait times would be reduced to 13 months for Alzheimer's patients because far fewer patients would need to see a specialist. Researchers also determined that if blood tests and brief cognitive assessments were used at the primary care level to rule in the possibility of an Alzheimer's diagnosis, wait times to understand eligibility for new treatments would fall to less than six months on average because of reduced demand for Alzheimer's specialists and the additional capacity now available for CSF or PET testing.

"Our results suggest using blood tests to identify potential candidates for treatments could make a significant difference in treating people with early Alzheimer's," said Soeren Mattke, M.D., D.Sc., lead author of the study and director of the Brain Health Observatory, at the University of Southern California, Los Angeles. "Currently, eligible patients are falling outside of the treatment window because it takes so long to receive a diagnosis. An easy-to-use blood test could help address that problem."

About the Alzheimer's Association International Conference® (AAIC®)
The Alzheimer's Association International Conference (AAIC) is the world's largest gathering of researchers from around the world focused on Alzheimer's and other dementias. As a part of the Alzheimer's Association's research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.
AAIC 2024 home page: www.alz.org/aaic/
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About the Alzheimer's Association®
The Alzheimer's Association is a worldwide voluntary health organization dedicated to Alzheimer's care, support and research. Our mission is to lead the way to end Alzheimer's and all other dementia — by accelerating global research, driving risk reduction and early detection, and maximizing quality care and support. Our vision is a world without Alzheimer's and all other dementia®. Visit alz.org or call 800.272.3900.

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- Sebastian Palmqvist, M.D., Ph.D., et al. Evaluation of the prospective use of blood biomarkers for Alzheimer's disease in primary and secondary care. (Funders: Alzheimer's Association, the National Institute of Aging)
- Gemma Salvadó, Ph.D., et al. Use of plasma p-tau217 as a pre-screening method for detecting amyloid-PET positivity in cognitively unimpaired participants: A multicenter study. (Funders: Alzheimer's Association, European Union's Horizon 2020 Research and Innovation Program under Marie Sklodowska-Curie action, Alzheimerfonden, Strategic Research Area MultiPark)
- Soeren Mattke, M.D., D.Sc., et al. Impact of a High-Performing Blood Test on Wait Times for Determination of Eligibility for a Disease-Modifying Alzheimer's Treatment in the U.S. (Funder: C2N Diagnostics)

*** AAIC 2024 news releases may contain updated data that does not match what is reported in the following abstracts.

Proposal ID: 88404

Evaluation of the prospective use of blood biomarkers for Alzheimer's disease in primary and secondary care.

Background: An accurate blood test for Alzheimer's disease (AD) could streamline the diagnostic work-up and treatment of AD. Our aim was to evaluate an AD blood test in primary and secondary care, using predefined biomarker cutoffs and prospective analyses of plasma samples.

Method: 940 prospective and unselected patients seeking medical evaluation for early cognitive symptoms were included. Plasma %p-tau217 and Aβ42/40 was measured using mass spectrometry and the Amyloid Probability Score-2 (APS2) combining these values was calculated. Predefined cutoffs were established in an independent training cohort and were applied to primary (n=307) and secondary care (n=300) cohorts comprised of patients undergoing cognitive evaluation where plasma samples were analyzed in single batches. The blood test was then evaluated prospectively in primary (n=100) and secondary (n=234) care patients where plasma samples were analyzed bi-weekly. The main outcome was amyloid status as determined by cerebrospinal fluid AD biomarker positivity.

Results: In primary care, 51% of patients were AD pathology positive and were diagnosed with the following: 25% subjective cognitive decline (SCD), 47% mild cognitive impairment (MCI), and 28% dementia. In secondary care 49% were AD pathology positive and diagnoses were 21% SCD, 43% MCI, and 36% dementia. Using single batch analyses in primary care, the AUC for APS2 was 0.97 (95% CI 0.95–0.99), PPV 91% (87–96%), and NPV 92% (87–96%); in secondary care, the AUC was 0.96 (0.94–0.98), PPV 88% (83–93%), and NPV 87% (82–93%). When samples were analyzed prospectively in primary care, the AUC was 0.97 (0.95–1.00), PPV 90% (81–99%), and NPV 90% (82–98%); in secondary care, the AUC was 0.97 (0.94–0.99), PPV 92% (86–97%), and NPV 89% (83–94%). Primary care physicians accurately identified AD in 58% of patients after a standard work-up versus 89% (83–95%) for APS2 (p<0.001). Dementia experts had a diagnostic accuracy of 74% (69–80%) versus 90% (86–94%) for APS2 (p<0.001). At AAIC, we will also present prospective data using plasma p-tau217 immunoassay-based tests.

Conclusions: Highly accurate AD blood tests might improve the diagnostic work-up of individuals with cognitive symptoms in primary and secondary care. Future studies are needed to further evaluate these tests prospectively in primary care of other countries.

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Proposal ID: 85773

Use of plasma p-tau217 as a pre-screening method for detecting amyloid-PET positivity in cognitively unimpaired participants: A multicenter study.

Background: Recent results from clinical trials in Alzheimer's disease (AD) emphasize the importance of treating early-stage disease. However, recruitment of preclinical AD participants is difficult due to the lack of symptoms, and the costs and/or invasiveness of established CSF and PET tests. We aimed to investigate whether plasma p-tau217 could be used to pre-screen cognitively unimpaired (CU)potential participants for amyloid-β (Aβ) pathology to improve the efficiency of clinical trial recruitment.

Method: We included 1,471 CU participants from eight cohorts (Table-1) with available plasma p-tau217, Aβ CSF biomarkers and Aβ-PET status (served as standard-of-truth). Plasma p-tau217 concentrations were z-scored based on Aβ-negative participants and harmonized across cohorts using neuro Combat. Cut-offs for plasma p-tau217 were derived in the BioFINDER-1 cohort (n=104) based on different specificity levels (90%, 95% and 97.5%) to maximize positive predictive values (PPV). These cut-offs were used in the other cohorts to assess the accuracy of plasma p-tau217 for detecting Aβ-PET positivity. Next, within plasma positive participants only, we evaluated the value of dichotomized Aβ CSF (based on established clinical thresholds) on assessing Aβ-PET positivity. All models included age and *APOE-ε4* carriership as covariates.

Result: 334 (24.4%) of participants were Aβ-PET positive. Using the *a priori* defined cutoffs, plasma p-tau217 categorization resulted in high PPVs (72.9%-81.2%), negative predictive values (NPVs, 82.5%-86.2%), and accuracy (82.4%-83.8%), with an overall rate of positivity between 10.9%-18.1% (Figure-1). When applying CSF biomarkers to the plasma positive participants in a second step, the PPVs increased up to 90.8%-95.3%, with NPVs ranging between 82.8%-86.7% and accuracies between 84.0%-87.3%, with a slight decrease in the proportion of overall positive cases (9.3%-14.3% from the original sample) given that the CSF positivity in the plasma positive participants ranged between 79.4%-85.2% (Figure-2).

Conclusion: Plasma p-tau217 can identify Aβ-PET positive CU individuals with PPVs reaching 81%, which can be further improved to PPVs of up to 95% with a subsequent CSF measurement. Plasma p-tau217 could be used, either as stand-alone biomarker, or as an initial step before CSF biomarkers (reducing their need by ~80-90%), for pre-screening in clinical trials of preclinical AD depending on the certainty needed for Aβ-PET positivity.

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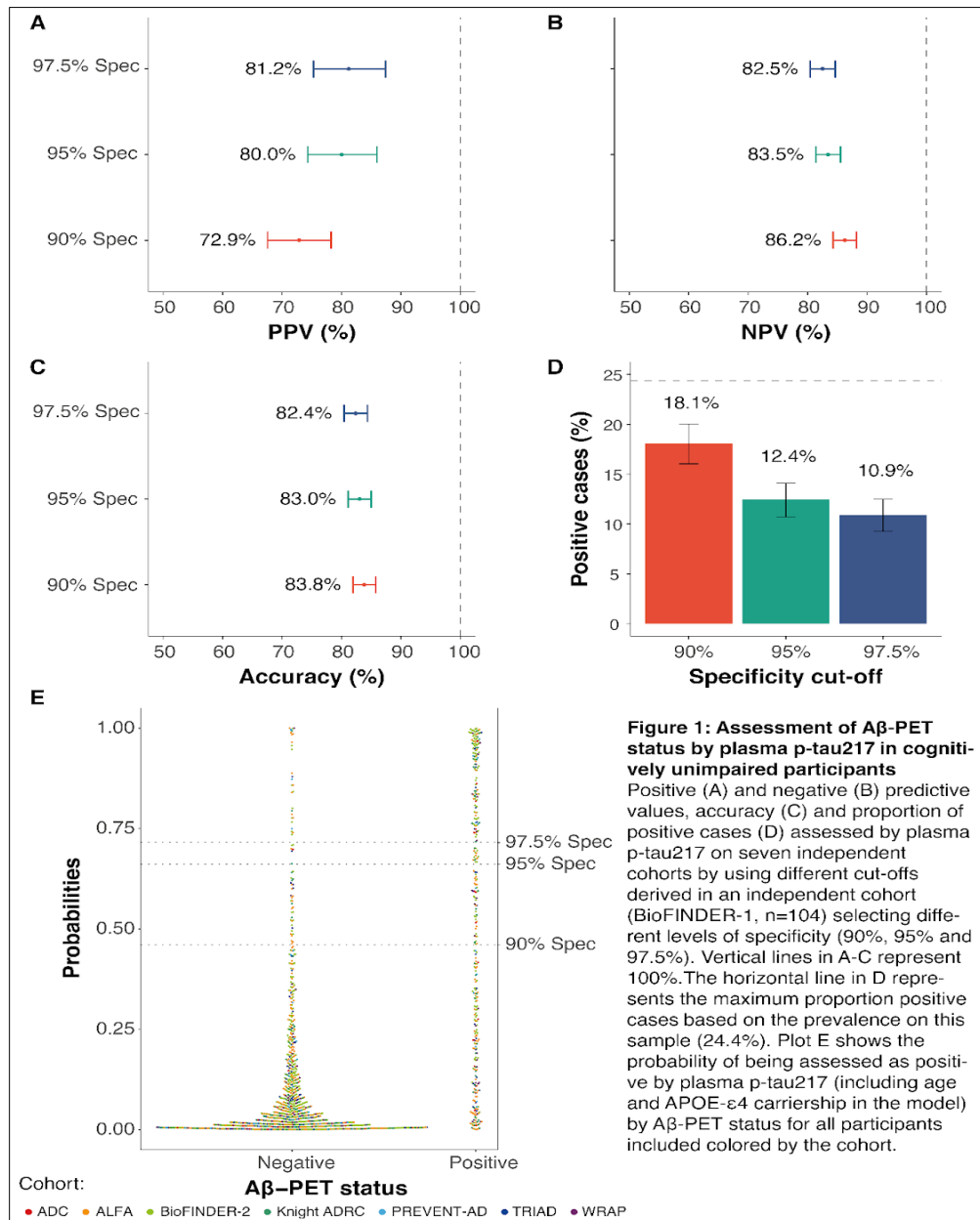Lund University, Lund, Sweden

Tables and Figures

	Overall (n=1,471)	BioFINDER-1 (n=104)*	BioFINDER-2 (n=591)	ALFA (n=341)	Knight ADRC (n=151)	TRIAD (n=103)	WRAP (n=89)	PREVENT-AD (n=56)	ADC (n=36)
Age, years	65.3 (9.25)	73.5 (5.23)	64.4 (11.7)	61.1 (4.66)	68.5 (6.08)	70.7 (6.39)	65.5 (6.26)	67.2 (4.65)	64.5 (6.94)
Women, n(%)	764 (51.9%)	69 (66.3%)	311 (52.6%)	213 (62.5%)	0 (0%)	61 (59.2%)	55 (61.8%)	39 (69.6%)	16 (44.4%)
APOE-ε4 carriership, n(%)	651 (44.3%)	43 (41.3%)	273 (46.2%)	185 (54.3%)	47 (31.1%)	29 (28.2%)	38 (42.7%)	22 (39.3%)	14 (38.9%)
Aβ-PET positive, n(%)	361 (24.5%)	43 (41.3%)	123 (20.8%)	54 (15.8%)	55 (36.4%)	40 (38.8%)	20 (22.5%)	12 (21.4%)	14 (38.9%)
Plasma p-tau217, z-score	0.432 (1.29)	0.435 (1.31)	0.423 (1.29)	0.442 (1.30)	0.432 (1.30)	0.431 (1.30)	0.442 (1.30)	0.442 (1.30)	0.442 (1.30)
Aβ CSF positive, n(%)	440 (29.9%)	37 (35.6%)	151 (25.6%)	116 (34.0%)	49 (32.5%)	35 (34.0%)	30 (33.7%)	11 (19.6%)	11 (30.6%)
Centiloids	8.76 (27.6)	9.22 (28.0)	8.36 (27.5)	9.07 (27.8)	8.86 (27.7)	9.20 (27.9)	-	-	-
Aβ-PET positivity method	-	Centiloids	Centiloids	Centiloids	Centiloids	Centiloids	SUVR	SUVR	VR
Aβ-PET tracer	-	[18F]flutemetamol	[18F]flutemetamol	[18F]flutemetamol	[11C]PIB/ [18F]florbetapir	[18F]AZD4694	[11C]PIB	[18F]flutemetamol	[18F]florbetapir
Plasma p-tau217 assay	-	Lilly	Lilly	Lilly	Lilly	Janssen	Lilly	Lilly	Lilly
Aβ CSF biomarker	-	Aβ42/40	Aβ42/40	Aβ42/40	Aβ42/40	Aβ42/40	Aβ42/40	Aβ42/p-tau181	Aβ42/p-tau181

Table 1: Participants' characteristics by cohort

Mean(SD) are shown unless otherwise specified. *BioFINDER-1 cohort was used only to derive plasma p-tau217 cut-offs.
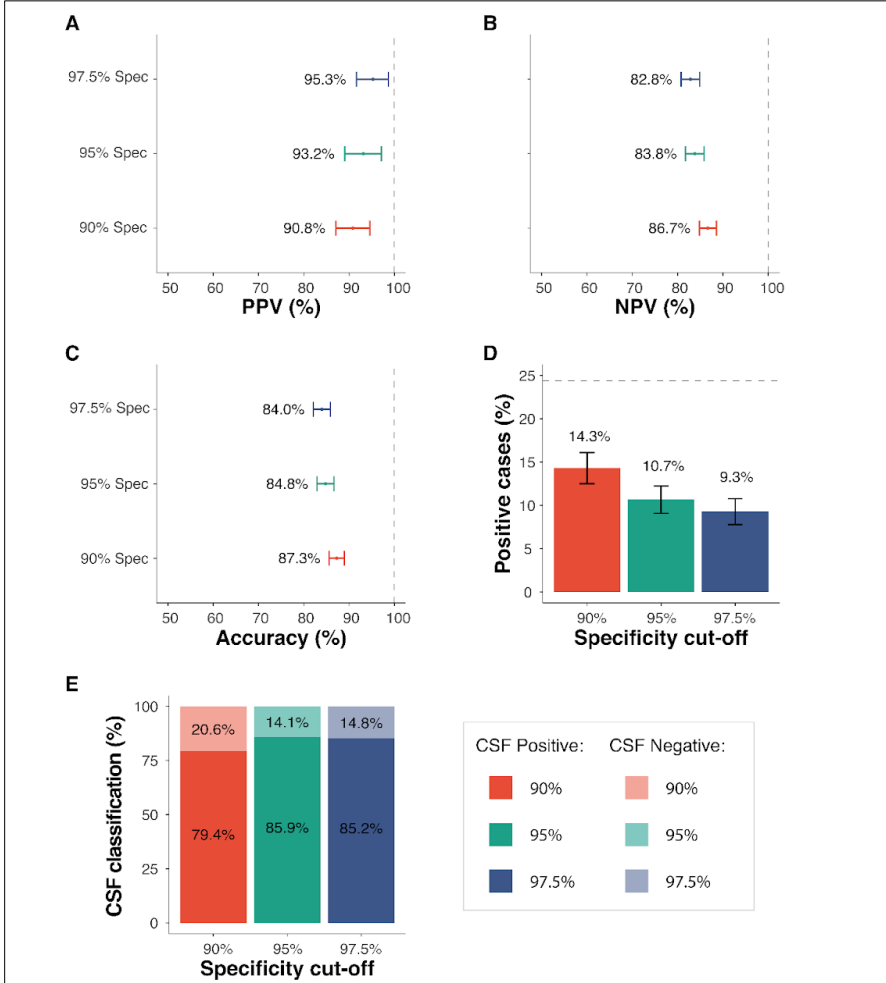Abbreviations: SUVR, standardized uptake value ratio; VR, visual read.

Figure 1: Assessment of Aβ-PET status by plasma p-tau217 in cognitively unimpaired participants
Positive (A) and negative (B) predictive values, accuracy (C) and proportion of positive cases (D) assessed by plasma p-tau217 on seven independent cohorts by using different cut-offs derived in an independent cohort (BioFINDER-1, n=104) selecting different levels of specificity (90%, 95% and 97.5%). Vertical lines in A-C represent 100%. The horizontal line in D represents the maximum proportion positive cases based on the prevalence on this sample (24.4%). Plot E shows the probability of being assessed as positive by plasma p-tau217 (including age and APOE-ε4 carriership in the model) by Aβ-PET status for all participants included colored by the cohort.

Figure 2: Assessment of Aβ-PET status by plasma p-tau217 followed by CSF measurement in cognitively unimpaired participants
Positive (A) and negative (B) predictive values, accuracy (C) and proportion of positive cases (D) assessed by plasma p-tau217 followed by dichotomized Aβ CSF on seven independent cohorts by using different plasma cut-offs derived in an independent cohort (BioFINDER-1, n=104) selecting different levels of specificity (90%, 95% and 97.5%). Vertical lines in A-C represent 100%. The horizontal line in D represents the maximum proportion positive cases based on the prevalence on this sample (24.4%). Plot E shows the probability of being assessed as positive by CSF in those participants assessed as plasma p-tau217 positive.

Proposal ID: 91612

Impact of a High-Performing Blood Test on Wait Times for Determination of Eligibility for a Disease-Modifying Alzheimer's Treatment in the U.S.

Background: As disease-modifying treatments for Alzheimer's disease (AD) are becoming available, concerns have been raised about wait times in the patient diagnostic journey due to a limited number of AD specialists and PET scanners. A high-performance blood test used in primary care settings has the potential to address this concern. We estimate the impact of such a test on wait times in the U.S.

Method: We use a Markov model to predict wait times for individuals identified as eligible for AD treatment, taking into account constrained capacity for AD specialist visits and confirmatory biomarker testing. We assume that individuals would undergo a brief cognitive assessment in primary care and, if indicative of early-stage cognitive impairment, be referred to a AD specialist under three scenarios:(1) no blood test, (2) blood test to rule out AD pathology, and (3) blood test to confirm AD pathology. We model the U.S. population aged 55+ from 2023 to 2032, assuming that 25% of all individuals, who have never been evaluated for cognitive decline, and 5%, who were previously found to be cognitively normal, would undergo a brief cognitive test. If found to have early-stage cognitive impairment and a blood test indicative of AD (if available), 80% would be referred to an AD specialist. The AD specialist would assess the patient and order biomarker testing for 90% of patients with confirmed early-stage cognitive impairment. Such biomarker testing would include CSF testing (10% and not capacity constrained) and PET imaging (90%). Patients would then return to the specialist to discuss test results and a treatment indication. If the blood test were used to confirm the AD pathology, patients would skip the first specialist visit.

Result: The figure shows the expected wait times for the three scenarios.

Conclusion: The introduction of a blood test into the AD diagnostic pathway could reduce wait times substantially and prevent eligible patients from falling outside the treatment window. Ongoing work will assess additional scenarios and patient pathways as well as their cost implications.

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Tables and Figures

Figure: Projected wait times for determination of treatment eligiblity