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Where Do Plasma Biomarkers fit in With Current Alzheimer's Disease Detection?

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ABSTRACT

Objectives: *We examine the clinical utility of plasma-based detection for Alzheimer's disease (AD) pathophysiology in older adults with mild cognitive impairment (MCI) and whether cognitive screening can inform when to use plasma-based AD tests.* ***Methods:*** *Seventy-four community-dwelling older adults with MCI had testing with plasma phosphorylated tau (p-tau) 217 and 181, positron emission tomography (PET) imaging for amyloid beta (Aβ), and cognitive assessment. Receiver operating characteristic (ROC) analysis was used to assess the diagnostic value of plasma p-tau.* ***Results:*** *Plasma p-tau217 distinguished MCI participants who had PET imaging evidence of Aβ accumulation from those without (AUC of 0.92, specificity of 0.96, and sensitivity of 0.90), outperforming plasma p-tau181 (AUC of 0.76, specificity of 0.87 and sensitivity of 0.59) for the same purpose. Of the 60 MCI participants that were amnestic, 22 were Aβ+. The 14 participants that were nonamnestic were all Aβ-.* ***Conclusions:*** *Our findings support the clinical use of plasma p-tau, particularly p-tau217, for patient detection of AD pathophysiology in older adults with amnestic MCI, but not in those who are nonamnestic.* (Am J Geriatr Psychiatry 2024; ■■:■■–■■)

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Highlights

- **What is the primary question addressed by this study?**
  Can blood biomarkers accurately identify older adults with mild cognitive impairment (MCI) who have imaging evidence of amyloid-beta (Aβ).
- **What is the main finding of this study?**
  Plasma p-tau217 accurately identifies older adults with MCI who have imaging evidence of Aβ, outperforming p-tau181 for the same purpose.
- **What is the meaning of the finding?**
  Plasma p-tau217 may be useful in clinical practice to identify older adults with MCI that have AD pathology, and cognitive screening may help guide when to perform this testing.

INTRODUCTION

The addition of blood-based biomarkers to conventional clinical assessments has the potential to improve the accurate and timely detection of Alzheimer's disease (AD).[1–3] The leading blood-based biomarkers include plasma tau phosphorylated at threonine-217 (p-tau217) and threonine-181 (p-tau181), which have demonstrated high accuracies to identify an abnormal cerebrospinal fluid (CSF) amyloid beta (Aβ)42/40 ratio or Aβ positron emission tomography (PET) scan.[4–7] With the implementation of anti-Aβ therapies, more scalable and cost-effective diagnostic approaches for biological evidence of AD in individuals who may be candidates for these interventions will be needed.[8] While commercially available blood tests for plasma p-tau biomarkers will be much less than the cost of Aβ PET and will be much more acceptable to patients than obtaining cerebrospinal fluid (CSF) via lumbar puncture, it is unclear when it might be appropriate to consider ordering these tests and how to interpret them when they become more widely available in clinical care. Plasma biomarkers have been evaluated in memory clinic[9] and research cohorts[4,5] but studies in broader clinical trial participants, especially outside of those sponsored by large pharmaceutical companies, as well as primary and secondary care, until recently,[10] have been lacking.

In this report, we evaluate the clinical value of plasma p-tau217 versus p-tau181 biomarkers in a therapeutic trial program for community-dwelling older adults with mild cognitive impairment (MCI) who had PET imaging for Aβ,[11] and both cognitive screeners and comprehensive cognitive assessment. An additional and novel purpose of this report is to identify potential cognitive screening instruments that could guide the future use of plasma p-tau biomarkers outside of a memory disorders clinic where older adults with MCI are less likely to convert to AD dementia and have less access to comprehensive neuropsychological testing.[12,13] For clinicians, rather than ordering plasma p-tau testing on all individuals who present with cognitive complaints, there may be individuals for whom ordering the test would be of little value. In contrast, there may be individuals for whom there is sufficient uncertainty that ordering the test would be helpful in guiding additional confirmatory testing with PET imaging for Aβ or lumbar puncture for CSF.

METHODS

This study included participants from the clinical trial, Lithium as a Treatment to Prevent Impairment of Cognition in Elders (LATTICE) (NCT03185208). The University of Pittsburgh Institutional Research Board approved all study procedures for the protection of human subjects and all participants provided written informed consent. This report consisted of baseline, prerandomization data from participants eligible for the clinical trial.

Participant inclusion/exclusion criteria. The study had the following inclusion criteria: 1) 60 years or older and 2) adjudicated diagnosis of MCI. Exclusion criteria included: 1) major psychiatric illness; 2) major neurologic illness; 3) contraindications to lithium; 4) inability to complete neuropsychological testing due to nonremediable impairment (e.g., blindness).

Recruitment methods. Prior to the Covid-19 pandemic, the study team employed a multipronged approach to recruitment, including in-person screening in the greater Pittsburgh community at senior centers, continuing education classes, senior communities, and senior housing. Additionally, we developed partnerships for referrals from the University of Pittsburgh Alzheimer's Disease Research Center (ADRC) and primary care practices. We also contacted former research participants. During the Covid-19 pandemic, in-person recruitment stopped and was replaced with Internet based approaches involving research registries and on-line and print media. Regardless of recruitment methods, all participants were from southwestern Pennsylvania.

Research Procedures

Neuropsychological Assessment: Prior to the Covid-19 pandemic, initial cognitive screens consisted of the Modified Mini-Mental Status (3MS),[14] Trail Making Test Parts A and B,[15] and the Quick Mild Cognitive Impairment (Qmci)[16] screen. To enter the study, individuals needed to score more than one standard deviation (SD) below expectation on Qmci, Trail Making Test (TMT) A, or TMT B and were excluded if two or more of the tests were more than two SDs below the mean. They were also excluded if they had a 3MS score below 84, which is roughly equivalent to a score of 25 on the Mini-Mental State Examination.[17] Qmci was normed for age and education. TMT was normed for age, education, and race.

During the Covid-19 pandemic, screens were conducted by telephone using the modified Telephone Interview for Cognitive Status (mTICS)[18] and the Hayling Sentence Completion Test (HSCT).[19] Participants had to score in the MCI range on the mTICS (Max score 50, >38 no cognitive disorder, 19−38 MCI range, <19 possible dementia) or have a scaled score of four or less on HSCT Section 1, Section 2, Section 2 # of errors, or overall score. These tests were not demographically normed.

Participants who met criteria for possible MCI with either cognitive screening method above underwent a comprehensive neuropsychological evaluation that included the following: Clinical Dementia Rating (CDR®),[20] Everyday Cognition Scale (Ecog) self- and informant-report, Wide Range Achievement Test-4th edition (WRAT-4).[21] Reading Subtest, Boston Naming Test, Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[22] (two alternate forms used, counter-balanced, to minimize practice effects), and subtests of the Delis−Kaplan Executive Function System(D-KEFS) (Verbal Fluency, Trail Making Test, Color Word Interference).[23] In addition, participants completed subtests of the Performance Assessment of Self-Care Skills (PASS), which is a performance-based measure of instrumental activities of daily living developed by occupational therapists.[24] The current study used the shopping, medication management, and bill paying sections as these have been determined to distinguish between persons without a cognitive disorder from those with a mild cognitive disorder.[25]

To assign a cognitive diagnosis, all neuropsychological assessments were reviewed at a Diagnostic Adjudication Conference attended by a neuropsychologist, a neurologist, and a geriatric psychiatrist. We used the National Alzheimer's Coordinating Center/Revised Petersen comprehensive criteria to diagnose MCI[26] Performance on cognitive tests were standardized using external normative sources adjusted for demographic factors as available (age, education, race, and/or gender) and were interpreted relative to estimated literacy (WRAT-IV), education, and occupational history, as well as available medical and clinical information. A diagnosis of MCI was conferred in participants who met the following criteria: 1) concern regarding a change in cognitive function as reported by the participant or informant on the Ecog, 2) objective evidence of cognitive impairment in one or more cognitive domains as indicated by performance of 1−2 SDs below expectation on either two tests within a single domain or three tests scattered across domains, 3) relatively preserved functional independence as demonstrated on the CDR and PASS, and 4) did not have cognitive performance in the dementia range. In cases where there was minimal report of cognitive symptoms (criteria #1) but sufficient evidence of MCI due to criteria #2−4 given the participant's educational and occupational history, an MCI diagnosis was conferred.

Plasma biomarkers: Plasma p-tau217 and p-tau181 were quantified using the ALZpath Simoa® p-Tau 217 V2 Assay Kit (#104371) and the Simoa p-tau181 Advantage kit (#104111), which is commercially available from Quanterix. The measurements were performed on an HD-X instrument manufactured by Quanterix in Billerica, MA, USA. Prior to the assays, plasma samples were thawed at room temperature, vortexed for

homogenization, and then centrifuged at 4000xg for 10 minutes to remove particulates. The measurement process was divided into two runs for the entire sample set. We used a single batch of reagents for this study to minimize any potential effect of batch variations. To evaluate the reproducibility of the assay, quality control samples with three different concentrations were analyzed at both the beginning and end of each run. The average coefficients of variation (CVs) within runs and between runs were 1.6% and 6.4%, respectively.

Imaging: Positron emission tomography (PET) and magnetic resonance (MR) imaging was performed on a Siemens Biograph mMR PET/MR system (Siemens Medical Systems USA, Malvern, PA) capable of simultaneous PET and three Tesla (3T) MR image acquisition. Indices of cerebral beta-amyloid (Aβ) load and status (positive/negative) were determined using [^{11}C]Pittsburgh Compound-B (PiB) PET imaging.[11] [^{11}C]PiB (15.0 mCi nominal) was injected intravenously outside of the scanner. Following a 40 minute uptake period, subjects were positioned in the scanner and [^{11}C]PiB PET image data acquired in list-mode over the 50−70 minutes postinjection interval. T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) and Dixon sequences were acquired simultaneously. [11C]PiB PET images were processed and analyzed as previously described using a FreeSurfer-based pipeline.[27] Global Aβ status was determined using a volume-weighed composite index of nine regions (GBL9) and a threshold GBL standardized update value ratio ≥ 1.346, which was determined by application of a sparse k-means clustering and resampling method[28] to [11C]PiB outcomes from a separate group of 61 cognitively unimpaired participants with 3T MR data.

Statistical Methods: Demographic and clinical characteristics were summarized using median and interquartile range (IQR) for continuous variables and frequency and percentage for categorical variables. Receiver operating characteristic (ROC) analysis was used to assess the diagnostic value of plasma p-tau. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC) were reported along with their 95% confidence intervals. An optimal cutoff was determined as the value with the maximum value of Youden's index (i.e., sensitivity + specificity − 1).[29] All analyses were conducted in R 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/).

RESULTS

The demographic and clinical characteristics of the 74 participants in this study are presented in Table 1. Forty-one (55%) participants were enrolled through

TABLE 1. Demographic and Clinical Characteristics of the Participants Based on Aβ- Versus Aβ+ Status

	Total (N = 74)	Aβ- (N = 52)	Aβ+ (N = 22)	Test statistic[a]	p-value
Age (Years)	70.8 (66.5−76.9)	69.1 (64.6−73.8)	75.8 (70.7−80.3)	323	<0.01
Education (Years)	16 (15−18)	16 (14−18)	16.5 (15.2−18)	444.5	0.12
Sex					0.13
Female	41 (55.4%)	32 (61.5%)	9 (40.9%)		
Male	33 (44.6%)	20 (38.5%)	13 (59.1%)		
Ethnicity					1.00
Hispanic	1 (1.4%)	1 (1.9%)	0 (0%)		
Not Hispanic	73 (98.6%)	51 (98.1%)	22 (100%)		
Race					0.48
White	64 (86.5%)	43 (82.7%)	21 (95.5%)		
Black or African American	9 (12.2%)	8 (15.4%)	1 (4.5%)		
Asian	1 (1.4%)	1 (1.9%)	0 (0%)		
Amnestic					0.01
No	14 (18.9%)	14 (26.9%)	0 (0%)		
Yes	60 (81.1%)	38 (73.1%)	22 (100%)		
p-tau217 (ng/mL)	0.3 (0.2−0.7)	0.3 (0.2−0.3)	0.8 (0.7−1)	96	<0.01
p-tau181 (ng/mL)	2.6 (2−3.7)	2.2 (1.8−3.1)	4.1 (2.6−4.6)	272	<0.01

Notes: Median and interquartile range (IQR) were reported for a continuous variable. Frequency and percentage were reported for a categorical variable.

p-values were calculated using Mann−Whitney test for a continuous variable and Fisher's exact test for a categorical variable, respectively.

[a] Mann−Whitney U test statistic for continuous variables.

on-line recruitment, 13 (18%) from community presentations, including two from local media presentations, two from word of mouth, and one from an advertisement poster, eight (11%) from the ADRC, seven (9%) from past or other research studies, and five (7%) from adult education programs at Carnegie Mellon University or the University of Pittsburgh. Participants who were Aβ+ or amnestic MCI (aMCI) were significantly older than Aβ- or nonamnestic MCI.

Among the 74 participants, 60 participants had aMCI (Table 2). Of these aMCI participants, 22 (37%) were Aβ+ by PET and 38 (63%) were Aβ-. All 22 participants that were Aβ+ were categorized as aMCI, with no nonamnestic MCI patient showing Aβ positivity. All participants who were nonamnestic MCI (n=14; 19%) were Aβ-. Three participants who were Aβ-, one aMCI and two nonamnestic MCI, had both the mTICS and Qmci during a transition from in-person to remote screening during the Covid-19 pandemic. mTICs scores significantly differed between Aβ- versus Aβ+ participants, while Qmci scores did not differ by Aβ group (Table 3).

We evaluated the accuracies of plasma p-tau biomarkers to identify a positive Aβ PET scan. The median (IQR) plasma p-tau217 and p-tau 181 levels significantly differed in Aβ+ versus Aβ- participants (Table 1 and Figure 1). Plasma p-tau217 had an AUC of 0.92, specificity of 0.96, and sensitivity of 0.90 to identify an abnormal Aβ PET scan, based on optimal within-cohort cutoff of 0.52. In contrast, plasma p-tau181 performed worse with an AUC of 0.76, specificity of 0.87 and sensitivity of 0.59, based on a within-cohort cutoff of 3.50 (Table 4 and Figure 2). The median (IQR) plasma p-tau217 and p-tau 181 levels in the aMCI versus nonamnestic MCI groups were not significantly different (Table 2). Among the Aβ- participants (N=52), mean (IQR) plasma levels of the aMCI (N=38) versus nonamnestic MCI (N=14) participants for p-tau217 was 0.3 (0.2−0.3) versus 0.3 (0.2 −0.3) pg/mL and, similarly, for p-tau181, 2.6 (1.6 −3.2) versus 2.3 (1.9−2.8) pg/mL.

DISCUSSION

In this study, we found that plasma p-tau217 is highly accurate in distinguishing an older adult clinical trial population with MCI who have PET imaging evidence of Aβ accumulation from those without, outperforming plasma p-tau181 for the same purpose. Our findings support clinical use of plasma p-tau, particularly p-tau217, for diagnostic evaluation for AD pathophysiology as suggested by other studies.[2,30–32] The question is how the test might be used in the clinical care in the future.

TABLE 2. Demographic and Clinical Characteristics of the Participants Based on Amnestic MCI Versus Nonamnestic MCI Status

	Total (N = 74)	Not amnestic (N = 14)	Amnestic (N = 60)	Test statistic[a]	p-value
Age (Years)	70.8 (66.5−76.9)	66.3 (62.8−69.4)	71.8 (67.2−78.4)	247	0.02
Education (Years)	16 (15−18)	16 (14−17.5)	16 (15−18)	350.5	0.33
Sex					0.56
Female	41 (55.4%)	9 (64.3%)	32 (53.3%)		
Male	33 (44.6%)	5 (35.7%)	28 (46.7%)		
Ethnicity					1.00
Hispanic	1 (1.4%)	0 (0%)	1 (1.7%)		
Not Hispanic	73 (98.6%)	14 (100%)	59 (98.3%)		
Race					0.17
White	64 (86.5%)	11 (78.6%)	53 (88.3%)		
Black or African American	9 (12.2%)	2 (14.3%)	7 (11.7%)		
Asian	1 (1.4%)	1 (7.1%)	0 (0%)		
Aβ					0.01
Negative	52 (70.3%)	14 (100%)	38 (63.3%)		
Positive	22 (29.7%)	0 (0%)	22 (36.7%)		
p-tau217 (ng/mL)	0.3 (0.2−0.7)	0.3 (0.2−0.3)	0.3 (0.2 - 0.7)	317	0.16
p-tau181 (ng/mL)	2.6 (2−3.7)	2.3 (2−2.8)	2.7 (2 - 4.2)	331	0.22

Notes: Median and interquartile range (IQR) were reported for a continuous variable. Frequency and percentage were reported for a categorical variable.

p-values were calculated using Mann−Whitney test for a continuous variable and Fisher's exact test for a categorical variable, respectively.

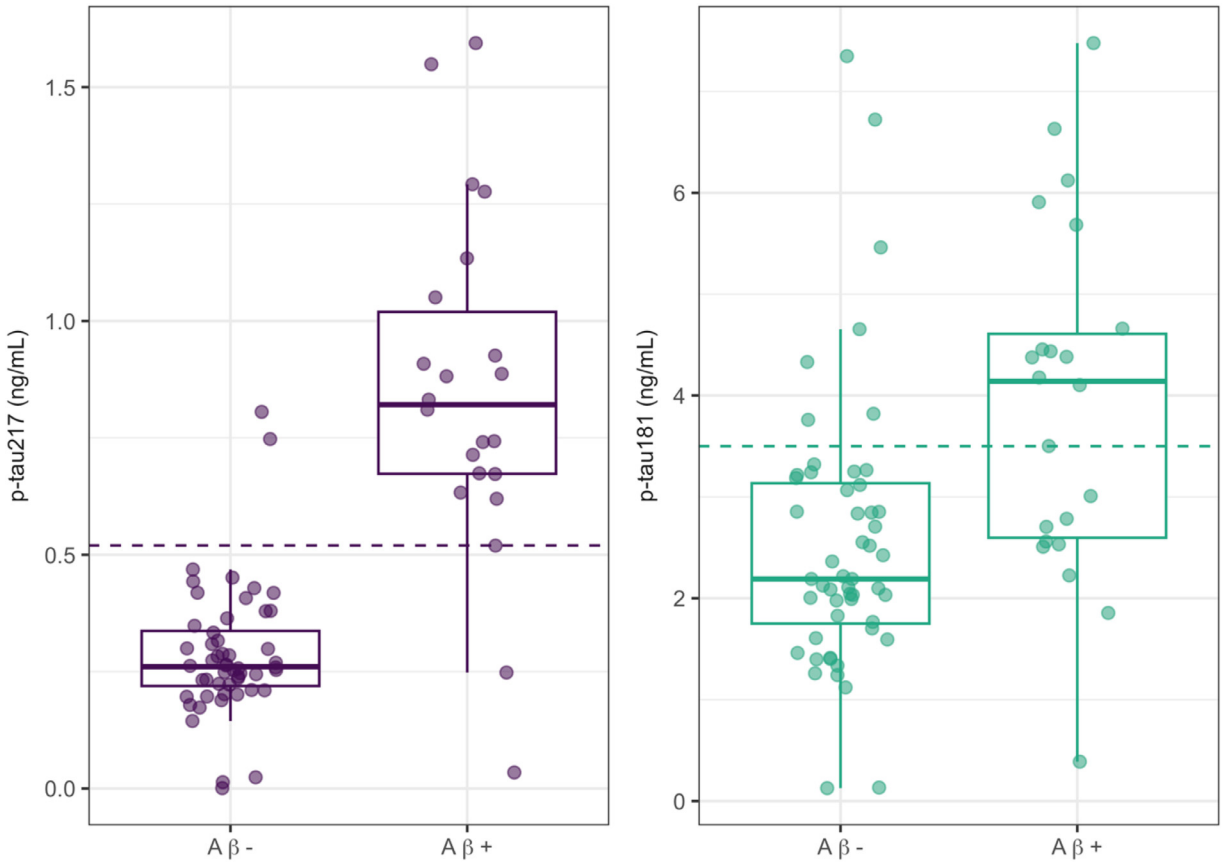
[a] Mann−Whitney U test statistic for continuous variables.

TABLE 3. mTICS and Qmci Scores by Aβ- Versus Aβ+ Status

	Aβ-			Aβ+	(comparing Aβ- vs Aβ+ groups)	
	Total N=52	MCI (nonamnestic) N=14	aMCI N=38	aMCI N=22	Test statistic	p-value
mTICS	35 (34–36) N=28	35.5 (33.8–36.3) N=8[a]	35 (34–36) N=20[a]	31 (29–33.8) N=10	225.5	<0.01
Qmci	62 (58 –66) N=27	66.5 (64.3–69.5) N=8[a]	59 (55–63.5) N=19[a]	61 (52–64.5) N=12	183	0.53

Notes: Median and interquartile range (IQR) were reported for a continuous variable.
p-values were calculated using Mann–Whitney test.
mTICS = modified Telephone Interview for Cognitive Status.
Qmci = Quick Mild Cognitive Impairment screen.
[a] Three participants who were A*β*-, one aMCI and two nonamnestic MCI, had both the mTICS and Qmci.

FIGURE 1. Boxplots of participants who are Aβ- or Aβ+ vs p-tau217 and p-tau181 levels with median, interquartile range, and min/max.



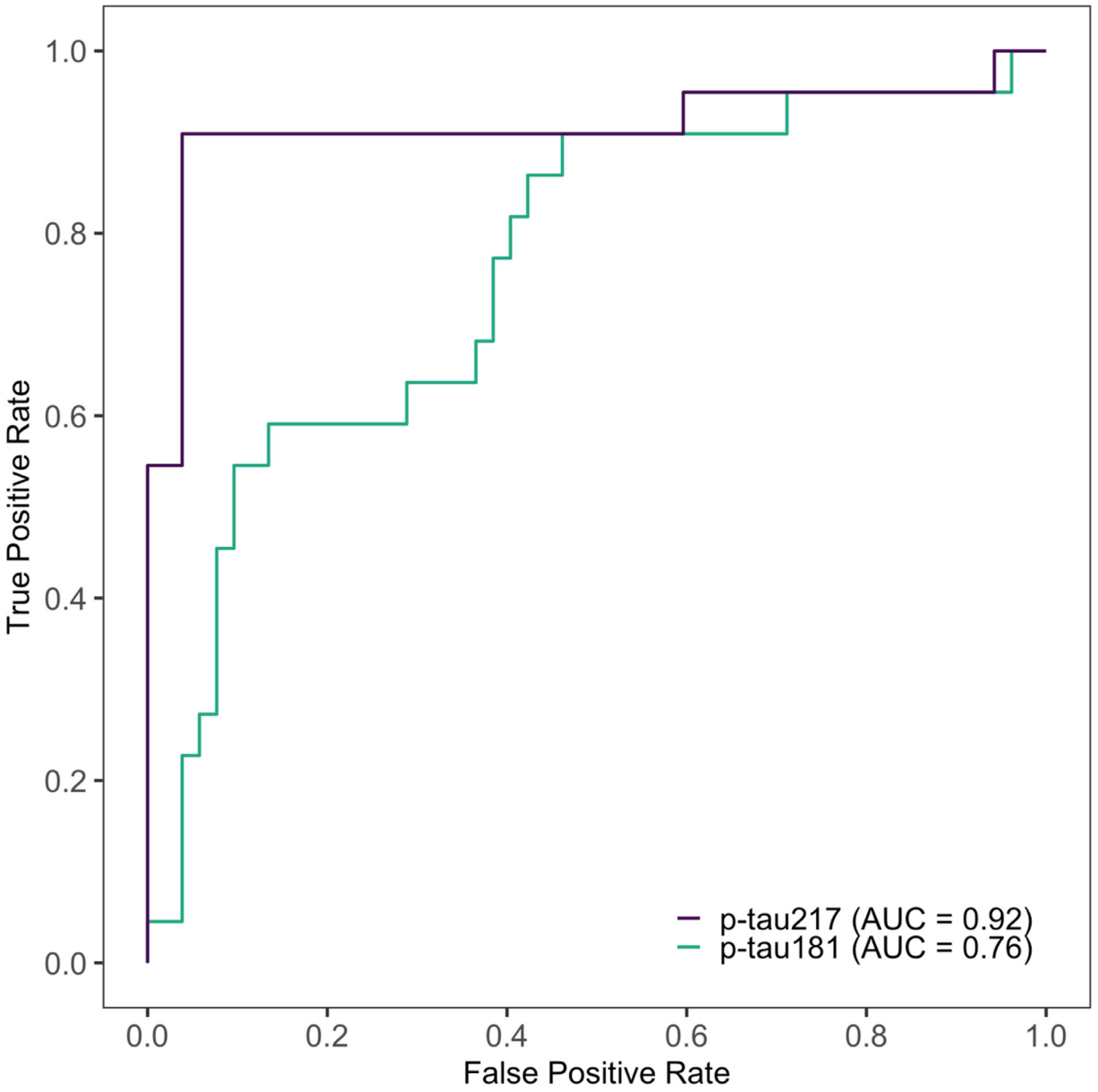
Note. Horizontal lines indicate cutoff values determined by Youden's index.

TABLE 4. Receiver Operating Characteristic Analysis

	Cutoff	Sensitivity	Specificity	PPV	NPV	AUC
ptau217	0.52	0.96 (0.91, 1.00)	0.91 (0.79, 1.00)	0.91 (0.79, 1.00)	0.96 (0.91, 1.00)	0.92 (0.82, 1.00)
ptau181	3.50	0.87 (0.77, 0.96)	0.59 (0.39, 0.80)	0.65 (0.44, 0.86)	0.83 (0.73, 0.93)	0.76 (0.64, 0.89)

Notes: Optimal cutoff value was determined as the value with the maximum value of Youden's index. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC) and their 95% confidence intervals are reported.

FIGURE 2. Receiver operating characteristic curves of p-tau217 and p-tau181 in classifying participants as Aβ- vs Aβ+.



A novel finding in our clinical trial cohort of 74 participants with MCI was that participants who were adjudicated to be *nonamnestic* had lower levels of p-tau217 and no evidence of Aβ accumulation on PET imaging. In contrast, participants with aMCI and within-cohort-derived cut-point of p-tau217 > 0.5 pg/mL were > 90% likely to be Aβ+ on PET. Based on our findings, individuals who have nonamnestic MCI or score >38 on the mTICS or score => 70 on the Qmci are likely to have low levels of p-tau217 and be Aβ- on PET. Hence, ordering a plasma-based blood test would not be clinically indicated. However, individuals with aMCI, scoring ≤ 38 on the mTICS, or scoring <70 on the Qmci may benefit from obtaining p-tau217 testing to further evaluate whether they have CNS amyloid as part of an evaluation for Alzheimer's type dementia. These findings should be replicated in other studies.

Both the mTICS and QMCI can be deployed in clinical practice with very brief training. The advantage of the mTICS is that it can be administered by telephone. In contrast, the Qmci is shorter and highly focused on AD-related impairments with list recall, semantic fluency, and immediate logical memory. In our study, amnestic individuals regardless of Aβ status scored similarly on the QMCI, while those with nonamnestic MCI scored higher. The mTICS is longer and more challenging, which may be why it was better at differentiating individuals with aMCI who are Aβ+ versus Aβ-.

Strengths of our report include community-dwelling participants who were recruited from the greater Pittsburgh area through mostly nonmemory clinic outreach sources. We have previously reported that participants recruited from specialty clinics have greater likelihood of having Alzheimer's type dementia.[33] When recruiting participants from the community, cognitive impairments are less likely to be early AD. A potential limitation here is that we used strictly cognitive screening and not functional ability as the initial entry point into the study, which may have inadvertently screened out some people with MCI. Additionally, the LATTICE clinical trial determined Aβ status using an SUVR cut-off rather than visual reads, which are standard in clinical settings. Nonetheless, this method has been shown to have good agreement with visual reads.[28] Further, being a pilot study, our results need to be evaluated and replicated in a much larger, diverse community-based sample of older adults, were an approach like this to be used outside of a memory disorders clinic.

Our findings suggest that in routine clinical practice, telephone screening, with an instrument such the mTICS, might help in identifying older adults with memory impairment who would benefit from further assessment with blood-based diagnostic tools for AD. If the goal is to identify individuals who would be candidates for anti-Aβ therapies, given the potential severity of side-effects with infusions of monoclonal antibodies, we foresee a multistep diagnostic protocol. This protocol could start with brief cognitive screening, followed by blood-based testing, then confirmation of brain Aβ status with lumbar puncture for CSF or PET imaging in uncertain cases (e.g., "negative" p-tau217 value, yet significant amnestic decline from baseline)."[34] The field is rapidly evolving with developing guidelines for the implementation anti-Aβ therapies. While telephone screening can be deployed now, future screening assessment might involve passive detection of key-click accuracy on smartphone, triggering an alert to healthcare providers, rather than telephone assessments as described in this report.[8] Moreover, our findings add to the body of work supporting the use of plasma p-tau217 to detect older adults with aMCI who have Aβ accumulation and therefore likely at high risk for converting to clinical AD.

DISCLOSURE

In the past 5 years, Dr. Lopez was a consultant for Novo Nordisk, Lundbeck, Eisai, Grifols, and Biogen. All other authors report no conflicts with any product mentioned or concept discussed in this article.

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AUTHOR'S CONTRIBUTIONS

The corresponding author (Ariel Gildengers) affirms listing everyone who has contributed significantly. All authors had 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) were involved in drafting the article or revising it critically for important intellectual content; and 3) gave final approval of the version to be published.

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DATA STATEMENT: The data has not been previously presented orally or by poster at scientific meetings.

References

1. Karikari TK, Ashton NJ, Brinkmalm G, et al: Blood phospho-tau in Alzheimer disease: analysis, interpretation, and clinical utility. Nat Rev Neurol 2022; 18:400–418
2. Gonzalez-Ortiz F, Kac PR, Brum WS, et al: Plasma phospho-tau in Alzheimer's disease: towards diagnostic and therapeutic trial applications. Mol Neurodegener 2023; 18:18
3. Kraemer HC, Schultz SK, Arndt S: Biomarkers in psychiatry: methodological issues. Am J Geriatr Psychiatry 2002; 10:653–659
4. Karikari TK, Pascoal TA, Ashton NJ, et al: Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. Lancet Neurol 2020; 19:422–433
5. Palmqvist S, Janelidze S, Quiroz YT, et al: Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. JAMA 2020; 324:772–781
6. Ashton NJ, Brum WS, Di Molfetta G, et al: Diagnostic accuracy of a plasma phosphorylated tau 217 immunoassay for Alzheimer disease pathology. JAMA Neurology 2024; 81:255–263
7. Janelidze S, Bali D, Ashton NJ, et al: Head-to-head comparison of 10 plasma phospho-tau assays in prodromal Alzheimer's disease. Brain 2022; 146:1592–1601
8. Whelan R, Barbey FM, Cominetti MR, et al: Developments in scalable strategies for detecting early markers of cognitive decline. Translational Psychiatry 2022; 12:473
9. Ashton NJ, Puig-Pijoan A, Milà-Alomà M, et al: Plasma and CSF biomarkers in a memory clinic: head-to-head comparison of phosphorylated tau immunoassays. Alzheimer's & Dementia 2023; 19:1913–1924
10. Palmqvist S, Tideman P, Mattsson-Carlgren N, et al: Blood biomarkers to detect Alzheimer disease in primary care and secondary care. JAMA 2024:e2413855
11. Klunk WE, Engler H, Nordberg A, et al: Imaging brain amyloid in Alzheimer's disease with Pittsburgh compound-B. Ann Neurol 2004; 55:306–319
12. Ganguli M, Jia Y, Hughes TF, et al: Mild cognitive impairment that does not progress to dementia: a population-based study. J Am Geriatr Soc 2019; 67:232–238
13. Mitchell AJ, Shiri-Feshki M: Rate of progression of mild cognitive impairment to dementia—meta-analysis of 41 robust inception cohort studies. Acta Psychiatr Scand 2009; 119:252–265
14. Teng EL, Chui HC: The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry 1987; 48:314–318
15. Reitan RM: Validity of the trail making test as an indicator of organic brain damage. Percept Mot Skills 1958; 8:271–276
16. O'Caoimh R, Gao Y, McGlade C, et al: Comparison of the quick mild cognitive impairment (Qmci) screen and the SMMSE in screening for mild cognitive impairment. Age and ageing 2012; 41:624–629
17. Ip EH, Pierce J, Chen SH, et al: Conversion between the Modified Mini-Mental State Examination (3MSE) and the Mini-Mental State Examination (MMSE). Alzheimers Dement (Amst) 2021; 13: e12161
18. Seo EH, Lee DY, Kim SG, et al: Validity of the telephone interview for cognitive status (TICS) and modified TICS (TICSm) for mild cognitive imparment (MCI) and dementia screening. Arch Gerontol Geriatr 2011; 52:e26–e30
19. Spitoni GF, Bevacqua S, Cerini C, et al: Normative data for the Hayling and Brixton tests in an Italian population. Arch Clin Neuropsychol 2018; 33:466–476
20. Morris JC: The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993; 43:2412–2414
21. Wilkinson GS, Robertson GJ: Wide range achievement test — Fourth edition: Professional manual. Lutz, FL: Psychological Assessment Resources, 2006
22. Wilk CM, Gold JM, Bartko JJ, et al: Test-retest stability of the repeatable battery for the assessment of neuropsychological status in schizophrenia. Am J Psychiatry 2002; 159:838–844
23. Delis DC, Kaplan E, Kramer JH: Delis-Kaplan Executive Function System. San Antonio, TX: The Psychological Corporation, a Harcourt Assessment Company, 2001
24. Chisholm D, Toto P, Raina K, et al: Evaluating capacity to live independently and safely in the community: performance assessment of self-care Skills. Br J Occup Ther 2014; 77:59–63
25. Rodakowski J, Skidmore ER, Reynolds CF 3rd, et al: Can performance on daily activities discriminate between older adults with normal cognitive function and those with mild cognitive impairment? J Am Geriatr Soc 2014; 62:1347–1352
26. Petersen RC: Mild cognitive impairment as a diagnostic entity. J Intern Med 2004; 256:183–194
27. Snitz BE, Tudorascu DL, Yu Z, et al: Associations between NIH Toolbox Cognition Battery and in vivo brain amyloid and tau pathology in non-demented older adults. Alzheimers Dement (Amst) 2020; 12:e12018
28. Cohen AD, Mowrey W, Weissfeld LA, et al: Classification of amyloid-positivity in controls: comparison of visual read and quantitative approaches. Neuroimage 2013; 71:207–215
29. Youden WJ: Index for rating diagnostic tests. Cancer 1950; 3:32–35
30. Ashton NJ, Janelidze S, Mattsson-Carlgren N, et al: Differential roles of Abeta42/40, p-tau231 and p-tau217 for Alzheimer's trial selection and disease monitoring. Nat Med 2022; 28:2555–2562

31. Therriault J, Servaes S, Tissot C, et al: Equivalence of plasma p-tau217 with cerebrospinal fluid in the diagnosis of Alzheimer's disease. Alzheimers Dement 2023; 19:4967–4977
32. Mila-Aloma M, Ashton NJ, Shekari M, et al: Plasma p-tau231 and p-tau217 as state markers of amyloid-beta pathology in preclinical Alzheimer's disease. Nat Med 2022; 28: 1797–1801
33. Gildengers A, Stoehr GP, Ran X, et al: Anticholinergic drug burden and risk of incident MCI and dementia: a population-based study. Alzheimer Dis Assoc Disord 2023; 37:20–27
34. Brum WS, Cullen NC, Janelidze S, et al: A two-step workflow based on plasma p-tau217 to screen for amyloid beta positivity with further confirmatory testing only in uncertain cases. Nat Aging 2023; 3:1079–1090