

FEATURED ARTICLE

Plasma p-tau₁₈₁ shows stronger network association to Alzheimer's disease dementia than neurofilament light and total tau

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Abstract

Introduction: We examined the ability of plasma hyperphosphorylated tau (p-tau)₁₈₁ to detect cognitive impairment due to Alzheimer's disease (AD) independently and in combination with plasma total tau (t-tau) and neurofilament light (NfL).

Brandon Frank and Madeline Ally contributed equally to this study as first authors.

Methods: Plasma samples were analyzed using the Simoa platform for 235 participants with normal cognition (NC), 181 with mild cognitive impairment due to AD (MCI), and 153 with AD dementia. Statistical approaches included multinomial regression and Gaussian graphical models (GGMs) to assess a network of plasma biomarkers, neuropsychological tests, and demographic variables.

Results: Plasma p-tau₁₈₁ discriminated AD dementia from NC, but not MCI, and correlated with dementia severity and worse neuropsychological test performance. Plasma NfL similarly discriminated diagnostic groups. Unlike plasma NfL or t-tau, p-tau₁₈₁ had a direct association with cognitive diagnosis in a bootstrapped GGM.

Discussion: These results support plasma p-tau₁₈₁ for the detection of AD dementia and the use of blood-based biomarkers for optimal disease detection.

KEYWORDS

Alzheimer's Disease, P-tau, Plasma biomarkers, Network analysis, Neuropsychology

1 | INTRODUCTION

The National Institute on Aging and Alzheimer's Association (NIA-AA) Research Framework defines Alzheimer's disease (AD) by its underlying pathophysiological processes.¹ In vivo biomarkers to measure AD neuropathological changes are critical for the early detection and treatment of AD.^{2–8} There are three classifications of biomarkers: brain amyloidosis (A), neurodegeneration (N), and tau pathology (T). Cerebrospinal fluid (CSF) and positron emission tomography (PET) imaging are gold standards for the detection of AD pathophysiology and provide a direct window into the central nervous system (CNS) to identify amyloid beta (A β) and hyperphosphorylated tau (p-tau).¹ Magnetic resonance imaging (MRI) is routine for the assessment of neuronal loss (e.g., atrophy),⁹ but CSF analysis for proteins such as total tau (t-tau) and neurofilament light (NfL) also provides insight into the severity of neurodegeneration.¹⁰ These approaches are viewed as invasive and/or expensive, calling on the need for scalable biomarker measurements with similar accuracy.^{1,11} The development of more practical biomarkers will permit large-scale implementation, both in research and clinical settings.

Through advancements in ultra-sensitive immunoassay and mass spectrometry technology, low abundance proteins can be detected in the blood, offering an exciting avenue for biomarker development.³ Plasma biomarkers of neurodegeneration have been of interest in the field of AD and AD-related dementias, especially NfL and t-tau, which reflect neuronal damage and cell death or degeneration.^{12,13} Sugarman et al.¹⁴ found that higher levels of plasma NfL discriminated AD dementia from those with normal cognition (NC) and mild cognitive impairment (MCI); in addition, plasma NfL was associated with disease severity and worse neuropsychological test performance across multiple domains, both at baseline and longitudinally. The results were less promising for plasma t-tau, which discriminated AD dementia from NC only, weakly correlated with neuropsychological function, and did not predict longitudinal outcomes. These results

are consistent with previous studies^{15–17} that support plasma NfL as a more accurate biomarker of AD neurodegeneration compared to t-tau.

Recent efforts have targeted immunoassay developments to detect p-tau in the blood.¹⁸ Hyperphosphorylated tau is a hallmark AD pathology and a precipitant of neurodegeneration and cognitive and functional decline in AD,^{3,9,19} making it a clear target for biomarker investigation to facilitate disease detection, diagnosis, and assess therapeutic response. With new developments in p-tau immunoassay technologies, plasma p-tau shows potential as a feasible biomarker of AD pathology.^{20,21} While multiple tau phospho-forms measured in CSF have support in detecting AD-type tau pathology, such as threonine 217 (p-tau₂₁₇) and threonine 231 (p-tau₂₃₁),^{22,23} threonine 181 (p-tau₁₈₁) has been widely characterized in early plasma biomarker analysis.^{3,24} Plasma p-tau₁₈₁ concentration is associated with worse neuropsychological test performance,^{25,26} correlates with longitudinal gray matter atrophy and increased odds of conversion to AD dementia,^{17,25,27–29} and distinguishes AD dementia from other neurodegenerative disorders (e.g., frontotemporal lobar degeneration).^{3,11,28,30,31} Furthermore, plasma p-tau₁₈₁ was highly predictive of AD pathology in a recent autopsy study; despite being taken 8 years prior to death, the biomarker was sensitive to *post mortem* AD tauopathy.²⁵

Research on the ability of plasma p-tau₁₈₁ to accurately detect the clinical manifestation of AD is still in its infancy. Existing studies have focused on p-tau₁₈₁ in isolation; the diagnostic utility of plasma p-tau₁₈₁ compared to and in conjunction with other plasma biomarkers remains unclear. This is an important limitation as a panel of plasma biomarkers will likely have optimal diagnostic accuracy^{32,33} as opposed to any one plasma protein in isolation.

The objective of this study was to examine the association between plasma p-tau₁₈₁ and cognitive diagnostic status (i.e., NC, MCI due to AD, and AD dementia), in isolation and in conjunction with plasma t-tau and NfL, as well as to test the association between plasma p-tau₁₈₁

and neuropsychological test performance. Our sample included participants from the Boston University (BU) Alzheimer's Disease Research Center (ADRC) Clinical Core. Sugarman et al.¹⁴ examined the usefulness of t-tau and NFL in the BU ADRC sample. We therefore leveraged both the sample and the previously quantified plasma biomarkers to examine the predictive validity of p-tau₁₈₁. We hypothesized that p-tau₁₈₁, t-tau, and NFL would independently discriminate participants with MCI and AD dementia from NC and that a panel of combined biomarkers would outperform each on its own. Our hypotheses were tested using traditional regression-based approaches (e.g., multinomial regression), in addition to a network modeling approach that assessed the conditional association of biomarkers, diagnostic and daily function variables, neuropsychological test performance, and relevant demographic variables in a single model.

Network theory suggests that entities such as neurological diseases are best understood from an inclusive approach, with various predictors and corollaries examined in concert. Network models represent a joint conditional probability distribution in which nodes (i.e., variables) are connected with edges (i.e., directed or undirected associations between variables).³⁴ These models are data-driven attempts to understand complex systems.³⁵ While under-utilized, network models have been used in research on biomarkers in AD,^{36–39} and most recently in one study of blood-based biomarkers.¹⁶ We contend that blood-based biomarkers will have optimal clinical utility as part of a panel of biological, cognitive, and behavioral data to assist with clinical detection and diagnosis of AD (i.e., to provide a full clinical profile of an individual patient).

2 | METHODS

2.1 | Participants and design

This study included participants from the BU ADRC Clinical Core Registry. The BU ADRC is one of ~30 centers funded by the NIA and provides data to the National Alzheimer's Coordinating Center (NACC) to promote collaborative research on AD. A detailed description of the BU ADRC is provided elsewhere.^{14,40–43} The present sample and study design are similar to the Sugarman et al.¹⁴ study that examined plasma NFL and t-tau in the BU ADRC. The BU ADRC follows older adults with and without cognitive impairment. All participants are English-speaking older adults with adequate visual acuity and hearing. Participants are excluded for a history of a serious mental illness (e.g., bipolar disorder, schizophrenia), non-AD/ADRD neurological disorders (e.g., brain tumor, multiple sclerosis), or medical conditions that preclude study participation. The BU ADRC protocol involves annual neurological examination, a clinical and medical interview, neuropsychological testing, measures of daily function, and other procedures.

Beginning in 2008, voluntary blood draws were initiated. All participants included in the current study provided a plasma sample, were evaluated, and received a diagnosis of NC, MCI due to AD, or AD dementia made during the same visit as samples were obtained. Neu-

RESEARCH IN CONTEXT

1. **Systematic review:** We reviewed the literature with traditional sources (e.g., PubMed). While several recent studies have examined plasma hyperphosphorylated tau (p-tau)₁₈₁, the clinical usefulness of blood-based biomarkers remains poorly understood. Network studies are also needed to examine associations between various predictors of Alzheimer's disease (AD) given its complex and mixed pathology.
2. **Interpretation:** The present results provide further evidence that plasma p-tau₁₈₁ provides unique diagnostic and clinical information and support its implementation in routine biomarker assessment related to the detection of AD dementia. The results also emphasize the importance of multiple biomarkers to capture different aspects of AD for optimal disease detection.
3. **Future directions:** Longitudinal studies are needed to clarify the clinical usefulness of plasma p-tau₁₈₁, particularly in terms of its role in the early detection of AD. Plasma biomarker–pathological correlation studies will also be essential for validation. In particular, a validated plasma biomarker panel could provide a less invasive, scalable means to transform clinical and research trials related to AD, and perhaps personal health care.

ropsychological and diagnostic data were used that were closest in time to the participants' initial blood draw, which did not necessarily correspond to their first ADRC visit. No follow-up data were included in the current study. Procedures were approved by the BU Medical Center Institutional Review Board. Participants (or their legally authorized representatives) provided written informed consent prior to participation in the BU ADRC protocol.

2.2 | Plasma biomarker collection and analysis

Non-fasting blood samples were collected for all participants. Blood was collected into plastic dipotassium ethylene diaminetetraacetic acid tubes, and processed according to standard procedures, with plasma aliquoted and frozen at -80°C. Frozen plasma aliquots were shipped on dry ice to the University of Gothenburg (Sweden) for batch analysis. Plasma p-tau₁₈₁ concentration was measured using an in-house single molecule array method on an HD-X analyzer (Quanterix), as previously described in detail.¹¹ The lower limit of quantification (LLoQ) was 1.0 pg/mL, with a dynamic range of 1.0 to 128.0 pg/mL. An in-house Simoa method was used to measure plasma NFL concentration (Quanterix), as described by Gisslén et al.⁴⁴ The LLoQ was 1.9 pg/mL, with a dynamic range of 1.9 to 1800 pg/mL. Plasma T-tau concentration was measured using Tau 2.0 kit and the HD-1 analyzer (Quanterix) with an LLoQ of

0.061 pg/mL and a dynamic range of 0.061 to 360 pg/mL. The measurements were performed in one round of experiments, using one batch of reagents. Intra-assay coefficients of variation were below 10% for all the biomarkers.

2.3 | Diagnostic procedures

All participants included in this study had a research cognitive diagnosis of NC, MCI due to AD, or AD dementia. Diagnoses were made by a BU ADRC multidisciplinary diagnostic consensus panel, after presentation and discussion of all examination and test findings (including review of structural MRI, if available); neuropsychological test scores; functional measures; as well as social, family, and medical history. Plasma biomarker data were not used in the adjudication of cognitive syndromes or suspected etiologies. Established criteria were used for AD dementia^{45,46} and MCI due to AD^{47,48} diagnoses. As an ADRC, we followed the NACC Uniform Data Set (UDS) diagnostic criteria for cognitive syndromes and suspected etiologies. There have been three versions of the UDS over time. For versions 1 and 2 of the UDS, AD dementia diagnoses were based on the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) diagnostic criteria.⁴⁵ For version 3, MCI and dementia diagnoses were based on the 2011 NIA-AA criteria.^{46,48} Regardless of the UDS version for MCI and dementia due to AD, MCI diagnoses were made based on evidence of impairment on neuropsychological test scores (i.e., 1.5 standard deviations below the normative mean) in the absence of functional impairment. A dementia diagnosis required the presence of functional impairment in the context of objective impairment on neuropsychological testing. Reported complaints and/or progressive worsening were required for both MCI and dementia diagnoses.

Dementia severity was rated using the Clinical Dementia Rating (CDR) Dementia Staging Instrument.^{49,51} CDR ratings encompass several domains including orientation, memory, judgment/problem solving, home and hobbies, community affairs, and personal care. CDR Sum of Boxes (CDR-SB) was used as the primary index from this measure following research suggesting comparable or improved diagnostic utility and desirable psychometric properties compared to the CDR global score.^{51,52} The Functional Activities Questionnaire (FAQ), a measure of instrumental activities of daily living, was also collected to monitor functional change over time.⁵³ CDR scores were informed by the report of a study partner and FAQ scores were based on the informant version of the measure.

2.4 | Neuropsychological tests

Consistent with the NACC-UDS,^{54,55} participants underwent a standardized neuropsychological examination to assess cognition across several domains. Tests administered and examined in this study included the Mini-Mental State Examination (MMSE), the Wechsler Adult Intelligence Scale-IV Digit Span (Forward and Backward; WAIS-

IV DSF and DSB), Trail Making Test Parts A and B (TMT-A and TMT-B, respectively), Semantic Fluency (Animal and Vegetable Fluency), the short form Boston Naming Test (BNT), and the Wechsler Memory Scale, Revised Logical Memory Delayed Recall (LM-II). Participants were also administered the Neuropsychological Assessment Battery (NAB) List Learning Test (Trials 1-3, Short Delay [SD], and Long Delay [LD]).⁵⁶ Neuropsychological outcomes included the primary indices of the tests that are routinely used and interpreted in both clinical and research settings. Scores reflect total correct for all measures except for TMT-A and B, for which total time was used (in seconds).

2.5 | Demographic variables and apolipoprotein E ε4 allele status

Demographic information was collected on all participants, including age (years), sex (male or female), self-reported race (re-coded as non-Hispanic White versus other), and years of education. Blood was drawn and used for apolipoprotein E (APOE) genotyping (ε4 carriers vs. non-carriers).

2.6 | Statistical analytic plan

Analyses were performed using the statistical programming language R (version 4.0.2; R Development Core Team).⁵⁷ We examined the performance of p-tau₁₈₁ in discriminating diagnostic groups relative to and in conjunction with plasma NfL and t-tau (NC, MCI due to AD, AD dementia). We assessed the relative contribution of p-tau₁₈₁ in a multinomial model with plasma NfL and t-tau, demographic variables (i.e., age, sex, self-reported race, and years of education), and APOE ε4 allele genotype status as additional predictors. The Hosmer and Lemeshow test⁵⁸ suggested no evidence of a poorly fitting model, $\chi^2(16, N = 569) = 12.18, P = 0.732$. Standardized effects are reported. Sensitivity models examined different combinations of the biomarkers, demographic variables, and APOE ε4 allele status to qualitatively compare receiver operating characteristic (ROC) analyses using the multiclass area under the curve (mAUC) statistic.⁵⁹ Discrimination accuracy was categorized according to guidelines suggested in Hosmer and Lemeshow (AUC = 0.50: no discrimination; AUC = 0.70–0.80: acceptable discrimination; AUC = 0.80–0.90: excellent discrimination; AUC ≥ 0.90: outstanding discrimination).⁶⁰ We assessed an additional model with all predictors and the CDR-SB as the criterion. Given the distribution of CDR-SB, we initially used Poisson regression.⁶¹ However, there was evidence for violation of residual deviance, $\chi^2(559, N = 569) = 1845.45, P < 0.001$. A negative binomial generalized linear model was thus used, which improved the model, $\chi^2(559, N = 569) = 516.24, P = 0.902$. Robust standard errors were interpreted and incidence rate ratios were computed using the delta method.⁶² Nonparametric bootstrapping of all models was conducted with 10,000 samples. Because missing data were rare (≤ 1%), pairwise deletion was used for regression models. Effect sizes were interpreted according to Cohen.⁶³

Partial correlation analyses using a Holm correction were conducted to examine the relationship between p-tau₁₈₁ and neuropsychological test performance.⁶⁴ These analyses controlled for demographic variables (age, sex, self-reported race, and years of education) and APOE ε4 allele status. These analyses were conducted to maintain consistency with our previous study involving this sample, and to compare and clarify our effects in the network models (see below).¹⁴ Pearson, polychoric, and polyserial correlations were used depending on whether the variables were continuous, ordinal, or mixed, respectively. We also conducted these analyses using Spearman's rank correlation for comparison. While there were a larger number of missing values for these variables (> 5% for 7/12 neuropsychological variables and > 10% for 1/12 variables), pairwise deletion was implemented to maintain consistency with our regression models. The association between neuropsychological measures and NfL and t-tau in this sample were previously reported by Sugarman et al.¹⁴

We conducted a network analysis to determine the variables with the greatest number and magnitude of associations in the network, and whether patterns or groupings of variables could be discerned. We also examined which variables would be most important and influential in determining or enabling the associations between other variables in the network (i.e., variables that would foster connections by serving as "central junctions" for other associations). We used undirected graphs due to (1) the cross-sectional nature of our data, (2) to avoid stringent assumptions regarding feedback loops, and (3) for clear interpretation of edge-weight parameters as the strength of unique associations.⁶⁵

Gaussian graphical models (GGMs) were estimated using the least absolute shrinkage and selection operator (LASSO)⁶⁶ regularization and a stepwise unregularized model search algorithm (ggmModSelect),⁶⁵ as well as, for comparison, a model retaining edges based on traditional statistical significance ($\alpha = 0.05$). The input matrix was estimated with Pearson, polychoric, and polyserial correlations depending on whether the variables were continuous, ordinal, or mixed, respectively. Variables in the model included plasma p-tau₁₈₁, NfL, and t-tau; diagnostic and functional measures (cognitive diagnostic status, CDR-SB, FAQ); demographic variables (age, sex, self-reported race, and years of education); APOE ε4 allele status; and neuropsychological measures.

Unlike the previously discussed analyses, there was concern for circularity in our network models as the CDR, FAQ, and neuropsychological measures were available during the multidisciplinary diagnostic consensus panels at which diagnoses were made. Causal graph models were not estimated due to these concerns for circularity. In addition, concerns were limited to retained edges between certain variables (i.e., the CDR, FAQ, and neuropsychological measures) and diagnosis. This relationship would not impact the retention of edges/effects between these variables and each other (e.g., the association between FAQ and CDR), as well as other variables included in the model (including biomarkers, which were our primary interest). As such, circularity would only impact 14 out of 529 possible direct effects. These effects were not interpreted. Given that the purpose of network theory is to include all relevant variables, we judged the value of inclusion to outweigh any limitation on the findings.

Network metrics of interest included node strength (i.e., the absolute sum of edge weights), closeness and between centrality (i.e., the average distance and shortest path length between nodes), and expected influence (the sum of edges extending from a given node).⁶⁷ These measures assess the importance and influence of variables for the overall network, rather than simply examining individual connections or edges. Network stability was assessed with a non-parametric bootstrap of standardized edge weights and a person-dropping bootstrap of centrality measures with 10,000 samples. Strength, closeness, and expected influence met established thresholds of stability (see supporting information for details).⁶⁵ The regularized network was interpreted due to the wide intervals of bootstrapped weights using the unregularized model search algorithm and the lack of sparsity in these results (see supporting information). Edge weights reflect a standardized partial correlation that has been regularized and bootstrapped.

Network fit was evaluated with the extended Bayesian information criterion (EBIC⁶⁸), the root mean square error of approximation (RMSEA⁶⁹) and the Tucker-Lewis index (TLI⁷⁰). Networks were visualized with eigenmodels, a latent modeling approach designed to create meaningful graphical space.⁷¹ Latent dimensions were estimated for the x- and y-axes (model-based decomposition and regression) with parameters derived from Markov chain Monte Carlo (MCMC) simulation. These dimensions can be interpreted in a similar manner to a traditional factor analysis.

3 | RESULTS

3.1 | Demographic and plasma biomarker results

A total of 569 individuals were included in this study, including 235 diagnosed as NC at the time of their plasma sample (41.3%), 181 diagnosed as MCI (31.8%), and 153 diagnosed as AD dementia (26.9%). The median age of the sample was 75 years (range 53–94) and 56.4% were female. Demographic and clinical characteristics are presented in Table 1. The range of values for blood-based biomarkers fell within the validated dynamic ranges for the assays (p-tau₁₈₁: 1.3–124.1 pg/mL; NfL: 3.0–121.5 pg/mL; t-tau: 0.6–37.7 pg/mL).

3.2 | Plasma biomarkers and diagnostic status

The initial multinomial model showed that higher p-tau₁₈₁ levels were associated with significantly higher conditional odds of an AD dementia diagnosis (conditional odds ratio [COR] = 1.47, 95% confidence interval [CI]: 1.06, 2.08, $P = .008$), but not an MCI diagnosis (COR = 1.13, 95% CI [0.89, 1.44], $P = .310$; see Table 2 and Figure S1 in supporting information). Higher NfL levels were also associated with significantly higher conditional odds of an AD dementia diagnosis (COR = 2.53, 95% CI [1.71, 3.65], $P < .001$), but not an MCI diagnosis (COR = 1.25, 95% CI [0.93, 1.67], $P = .115$). Higher t-tau levels were not associated with higher conditional odds of an AD dementia or MCI diagnosis.

TABLE 1 Demographic and clinical characteristics by diagnostic group

	NC (n = 235)	MCI (n = 181)	AD dementia (n = 153)
Demographic variables			
Age	72.38 (7.69)	74.96 (7.25)	76.82 (8.13)
Sex (male: female)	37:63	42:58	56:44
Race (non-Hispanic White: non-White)	90:10	75:25	92:8
Years of education	16.56 (2.54)	15.52 (2.77)	14.95 (2.95)
Genetic			
APOE ε4 allele status (yes: no)	33:67	33:67	58:42
Neuropsychological measures			
Animal Fluency	22.08 (5.27)	16.98 (5.13)	10.45 (5.37)
BNT	28.23 (1.65)	25.31 (4.49)	20.27 (7.23)
DSF	6.99 (0.93)	6.40 (1.03)	6.13 (1.21)
DSB	5.30 (1.23)	4.64 (1.25)	3.61 (1.42)
LM-II	14.70 (3.74)	11.02 (4.66)	2.34 (3.44)
MMSE	29.39 (0.91)	28.20 (1.68)	21.12 (6.21)
NAB Trials 1-3	23.69 (4.53)	18.21 (5.01)	9.94 (4.91)
NAB SD	8.39 (2.36)	5.32 (2.59)	1.24 (1.75)
NAB LD	8.41 (2.41)	4.91 (2.79)	0.72 (1.46)
TMT-A	28.78 (8.80)	36.97 (18.03)	63.08 (38.88)
TMT-B	69.50 (28.47)	127.76 (78.14)	223.30 (88.42)
Vegetable Fluency	15.71 (3.97)	12.93 (3.89)	6.64 (3.98)
Functional			
CDR Sum of Boxes	0.07 (0.26)	0.37 (0.64)	6.53 (4.27)
FAQ	0.23 (1.99)	0.65 (1.89)	14.27 (9.74)
Biomarkers			
NfL	15.43 (10.51)	17.61 (9.89)	26.57 (17.45)
P-tau ₁₈₁	16.05 (11.07)	18.10 (10.01)	25.92 (15.62)
T-tau	3.20 (2.73)	3.29 (2.39)	3.70 (2.99)

Note. Values reflect mean or proportion, with standard deviation in parentheses.

Abbreviations: AD, Alzheimer's disease; BNT, Boston Naming Test; CDR, Clinical Dementia Rating; DSF & DSB, Digit Span Forward and Backward; FAQ, Functional Activities Questionnaire; LM-II, Logical Memory Delayed Recall; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NAB SD & LD, Neuropsychological Assessment Battery List Learning Test, Short and Long Delay; NC, normal control; NfL, neurofilament light; P-tau₁₈₁, hyperphosphorylated tau; TMT-A & B, Trail Making Test; Parts A and B; T-tau, total tau.

In the full model (i.e., demographics, APOE ε4 allele status, and all plasma biomarkers), the accuracy for discriminating diagnostic groups fell in the "acceptable" range (mAUC = 0.749). In a model with demographic variables and APOE ε4 allele status (i.e., without plasma biomarkers), the discrimination accuracy was at the bottom of the "acceptable" range (mAUC = 0.706). Models with plasma biomarkers, and without demographic variables and APOE ε4 allele status, all fell below the range of "acceptable" discrimination (Table 3). Models with individual plasma biomarkers, along with demographic variables and APOE ε4 allele status, fell in the range of "acceptable" discrimination: NfL, mAUC = 0.743; p-tau₁₈₁, mAUC = 0.730; and t-tau, mAUC = 0.711. In models with and without p-tau₁₈₁, the independent contribution of t-tau was negligible (i.e., adding it to the model with

demographic variables and APOE ε4 allele status resulted in a ΔmAUC of 0.005, whereas removing it from models resulted in a ΔmAUC between 0.000 and 0.002).

3.3 | Plasma biomarkers and CDR-SB

The negative binomial generalized linear model showed a statistically significant effect of p-tau₁₈₁ on CDR-SB (incident rate ratio [RR] = 1.29, 95% CI [1.01, 1.39], *P* = .003; see Table 4). Plasma NfL was also associated with CDR-SB (RR = 1.72, 95% CI [1.70, 2.59], *P* < .001). In contrast, there was no statistically significant effect of t-tau on CDR-SB (RR = 1.07, 95% CI [1.00, 1.30], *P* = .345).

TABLE 2 Multinomial model contrasting the normal control group versus each of the other groups (N = 569)

	NC vs.	β_z	COR	95% CI	Wald Z	P
(Intercept)	MCI	0.067	1.07	(0.06, 17.27)	0.047	0.962
	AD dementia	1.811	6.12	(0.16, 205.35)	1.115	0.265
P-tau ₁₈₁	MCI	0.126	1.13	(0.89, 1.44)	1.015	0.310
	AD dementia	0.385	1.47	(1.06, 2.08)	2.650	0.008**
T-tau	MCI	0.056	1.06	(0.83, 1.35)	0.491	0.624
	AD dementia	0.184	1.20	(0.91, 1.58)	1.402	0.161
NfL	MCI	0.220	1.25	(0.93, 1.67)	1.578	0.115
	AD dementia	0.929	2.53	(1.71, 3.65)	5.573	<0.001***
Age	MCI	0.024	1.02	(0.99, 1.06)	1.491	0.136
	AD dementia	0.018	1.02	(0.98, 1.06)	0.979	0.327
Race	MCI	1.067	2.91	(1.51, 5.52)	3.578	<0.001***
	AD dementia	-0.300	0.74	(0.27, 1.83)	-0.696	0.487
Sex	MCI	-0.394	0.67	(0.43, 1.05)	-1.809	0.070
	AD dementia	-1.072	0.34	(0.21, 0.59)	-4.171	<0.001***
Years of education	MCI	-0.124	0.88	(0.82, 0.96)	-3.060	0.002**
	AD dementia	-0.232	0.79	(0.72, 0.88)	-4.897	<0.001***
APOE ϵ 4 allele status	MCI	0.037	1.04	(0.67, 1.64)	0.162	0.871
	AD dementia	1.125	3.08	(1.80, 5.12)	4.394	<0.001***

Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; CI, confidence interval; COR, conditional odds ratio; MCI, mild cognitive impairment; NC, normal control; NfL, neurofilament light; P-tau₁₈₁, hyperphosphorylated tau; T-tau, Total tau.

TABLE 3 Multiclass area under the curve statistics for multinomial models including blood-based biomarkers, demographic variables, and APOE ϵ 4 allele status

Model	mAUC	Descriptor
All predictors	0.749	Acceptable
Demographic variables and APOE status	0.706	Acceptable
P-tau ₁₈₁ only	0.634	Below
T-tau only	0.543	Below
NfL only	0.658	Below
P-tau ₁₈₁ , NfL, demographic variables, and APOE ϵ 4 allele status	0.748	Acceptable
P-tau ₁₈₁ , t-tau, demographic variables, and APOE ϵ 4 allele status	0.730	Acceptable
NfL, t-tau, demographic variables, and APOE ϵ 4 allele status	0.745	Acceptable
P-tau ₁₈₁ , demographic variables, and APOE ϵ 4 allele status	0.730	Acceptable
T-tau, demographic variables, and APOE ϵ 4 allele status	0.711	Acceptable
NfL, demographic variables, and APOE ϵ 4 allele status	0.743	Acceptable

Note. Models compare AD dementia and MCI due to AD groups to normal controls. Descriptors based on Hosmer and Lemeshow.⁶⁰

Abbreviations: APOE, apolipoprotein E; mAUC, multiclass area under the curve statistic; NfL, neurofilament light; P-tau₁₈₁, hyperphosphorylated tau; T-tau, total tau. Demographic predictors included age, race, sex, years of education, and APOE ϵ 4 allele status (carriers vs. non-carriers).

3.4 | P-tau₁₈₁ and neuropsychological test performance

Partial correlation models that controlled for demographic variables and APOE ϵ 4 allele status showed that p-tau₁₈₁ was associated with all neuropsychological measures except TMT-A. Higher p-tau₁₈₁ was associated with lower MMSE scores ($r = -0.20$, 95% CI [-0.28, -0.12],

$P < .001$), DSF ($r = -0.11$, 95% CI [-0.19, -0.02], $P = .01$), DSB ($r = -0.09$, 95% CI [-0.17, -0.01], $P = .03$), animal fluency ($r = -0.18$, 95% CI [-0.26, -0.10], $P < .001$), vegetable fluency ($r = -0.15$, 95% CI [-0.23, -0.07], $P < .001$), BNT ($r = -0.17$, 95% CI [-0.25, -0.09], $P < .001$), LM-II ($r = -0.16$, 95% CI [-0.24, -0.08], $P < .001$), NAB Trial 1-3 ($r = -0.14$, 95% CI [-0.22, -0.06], $P < .001$), NAB SD ($r = -0.14$, 95% CI [-0.22, -0.06], $P < .001$), and NAB LD ($r = -0.13$, 95% CI [-0.21, -0.05],

TABLE 4 Negative binomial generalized linear model predicting CDR Sum of Boxes (N = 569)

	β_z	SE	RR	95% CI	P
(Intercept)	1.77	1.16	5.85	(0.51, 48.31)	0.128
P-tau ₁₈₁	0.25	0.09	1.29	(1.01, 1.39)	0.003**
T-tau	0.06	0.07	1.07	(1.00, 1.30)	0.345
NfL	0.54	0.11	1.72	(1.70, 2.59)	<0.001***
Age	0.00	0.01	1.00	(0.98, 1.03)	0.951
Race	-0.61	0.25	0.54	(0.37, 0.99)	0.015*
Sex	-0.37	0.16	0.69	(0.38, 0.70)	0.018*
Years of education	-0.10	0.03	0.91	(0.85, 0.95)	0.001**
APOE ϵ 4 allele status	0.58	0.15	1.78	(1.42, 2.60)	<0.001***

Abbreviations: APOE, apolipoprotein E; CDR, Clinical Dementia Rating; CI, confidence interval; NfL, neurofilament light; P-tau₁₈₁, hyperphosphorylated tau; RR, incident rate ratio; SE, robust standard error; T-tau, total tau.

$P < .001$), as well as slower performance on TMT-B, $r = 0.13$, 95% CI [0.05, 0.21], $P < .001$. These findings were consistent with models using Spearman's rank correlation (see supporting information).

3.5 | Network analysis

Neuropsychological measures loaded highly on a latent dimension in the regularized GGM, especially MMSE, NAB Trials 1-3, NAB SD and LD, and LM-II (Figure 1). The second latent dimension was comprised primarily of CDR-SB and FAQ scores (i.e., functional status and disease progression). The biomarker variables loaded similarly on the two latent dimensions and were clustered near TMT-A and TMT-B; age; sex; APOE ϵ 4 allele status; and, to a lesser extent, cognitive diagnostic status. These groupings are suggestive of "subnetworks" that could be loosely interpretable as factors (i.e., "microsystems" of the network). Out of 529 possible edges, 138 (26%) were retained after regularization and 45 (8%) were retained after bootstrapping, suggesting an adequately sparse model. Thus, we judged that the network adequately controlled for false positive associations. There was also adequate model fit, $\chi^2(184, N = 569) = 620.46$, EBIC = 27,444.53, RMSEA = 0.06, TLI = 0.95.

Cognitive diagnostic status was connected to several edges (see supporting information), including TMT-B ($\beta_z = 0.18$, 95% CI [0.11, 0.25], animal fluency ($\beta_z = -0.08$, 95% CI [-0.14, -0.01]), vegetable fluency ($\beta_z = -0.09$, 95% CI [-0.16, -0.03]), LM-II ($\beta_z = -0.21$, 95% CI [-0.29, -0.13]), NAB SD ($\beta_z = -0.07$, 95% CI [-0.14, -0.01]), and NAB LD ($\beta_z = -0.17$, 95% CI [-0.25, -0.10]). This was expected given that neuropsychological test performance is used to assist with adjudication of consensus diagnostic status. More importantly, cognitive diagnosis was only connected to p-tau₁₈₁ ($\beta_z = 0.07$, 95% CI [0.01, 0.12]) and not plasma NfL or t-tau. None of the neuropsychological measures were connected to p-tau₁₈₁. NfL was connected to FAQ scores ($\beta_z = 0.08$, 95% CI [0.02, 0.13]) and animal fluency ($\beta_z = -0.09$, 95% CI [-0.16, -0.03]). The discrepancy between these findings and results from partial correlation models reflects regularization (i.e., the removal of con-

nections that weaken the overall predictive accuracy of the network model).

Among centrality measures, CDR-SB and cognitive diagnostic status ranked highly for closeness and betweenness centrality (Figure 2). Vegetable fluency and NAB Trials 1-3 ranked highly for expected influence. None of the biomarkers ranked highly for closeness centrality. However, p-tau₁₈₁ ranked relatively highly for betweenness centrality and expected influence and NfL ranked highly for betweenness centrality. These measures, therefore, can be considered important and/or influential as "central junctions" for other connections in the overall network. In contrast, t-tau was not highly ranked on any centrality measure. There were relatively modest differences in centrality measures between the models derived from regularization, stepwise model selection, and statistical significance.

4 | DISCUSSION

The present study evaluated the ability of plasma p-tau₁₈₁ to detect cognitive impairment due to AD among 569 community-dwelling older adults from the BU ADRC Clinical Core. This study expanded on our previous work on plasma NfL and t-tau¹⁴ by examining these plasma biomarkers in conjunction with plasma p-tau₁₈₁; we examined their association with clinical diagnosis and additional characteristics of the sample including dementia severity, functioning, and neuropsychological test performance. Higher levels of plasma p-tau₁₈₁ accurately discriminated participants with NC from AD dementia but not MCI due to AD. Models that included plasma biomarkers in combination with demographic variables and APOE ϵ 4 allele status provided the greatest predictive accuracy of diagnostic groups, supporting arguments for a focus on combined biomarkers in AD research.⁷² Higher plasma p-tau₁₈₁ concentrations were associated with greater dementia severity and worse neuropsychological test performance. We did not find adequate discrimination for diagnosis of MCI due to suspected AD, which is inconsistent with previous studies examining p-tau₁₈₁.^{27,11,73}

In addition to traditional regression models, we examined a network model of associations among plasma biomarkers, diagnostic and

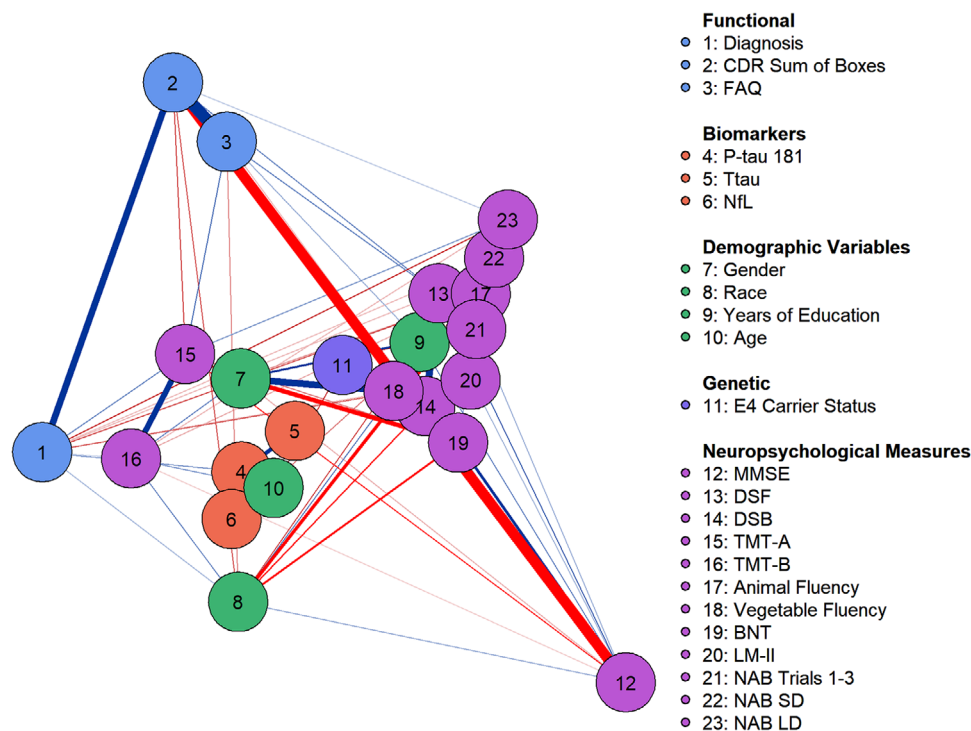


FIGURE 1 Gaussian graphical model with least absolute shrinkage and selection operator regularization. Latent dimensions were estimated with Markov chain Monte Carlo simulation. Nodes on the right side of the visualization load highly on dimension 1 and nodes toward the top load highly on dimension 2. Node location reflects variable loading on the two latent dimensions. Positive associations are depicted as blue. Edge width reflects the magnitude of association and edge saturation (i.e., darkness) reflects the likelihood of the association. Node colors reflect artificial groupings from the legend. BNT, Boston Naming Test; CDR, Clinical Dementia Rating; DSF & DSB, Digit Span Forward and Backward; FAQ, Functional Activities Questionnaire; LM-II, Logical Memory Delayed Recall; MMSE, Mini-Mental State Examination; NAB SD & LD, Neuropsychological Assessment Battery List Learning Test, Short and Long Delay; NfL, neurofilament light; P-tau₁₈₁, hyperphosphorylated tau; TMT-A & B, Trail Making Test, Parts A and B; Ttau, total tau

functional measures, demographic variables, APOE $\epsilon 4$ allele status, and neuropsychological measures. Network models provide a data-driven method to investigate complex systems and to examine numerous associations simultaneously. Unlike plasma NfL or t-tau, plasma p-tau₁₈₁ showed a direct relationship with cognitive diagnostic status in the model. Plasma p-tau₁₈₁ was also connected to both NfL and t-tau, which were indirectly associated with cognitive diagnostic status. Such connections provide tentative support for complex biological interactions among p-tau₁₈₁, myelin and axonal loss, and neuronal dysfunction in the clinical manifestation of AD (as reviewed in Nasrabady et al.¹⁹). However, neurodegeneration would perhaps best be characterized by a longitudinal graph model, such as a hidden Markov model,^{74,75} in which causal inferences could be explicit. Future longitudinal studies should confirm these findings and pathways.

Unlike t-tau, p-tau₁₈₁ and NfL ranked highly on network centrality measures, suggesting that they explained important variance in direct and indirect associations within the network. That is, these plasma biomarkers were highly influential in fostering connections and impacting other nodes. In addition, analysis of latent dimensions in the network suggested groupings based on (1) objective cognitive performance and (2) functional status/disease progression. Plasma biomarkers were associated with these groupings in a pattern similar to the

node reflecting research diagnosis (i.e., AD dementia, MCI due to AD, and NC), suggesting the biomarkers provide important and unique information on both sets of clinical characteristics. Plasma p-tau₁₈₁ was central to the network more broadly and with more stability than NfL. In contrast, t-tau had little impact or relevance to direct and indirect associations in the network. In sum, these findings suggest that plasma p-tau₁₈₁ and NfL captured important aspects of the clinical profile in our sample, not otherwise captured by demographic variables and APOE $\epsilon 4$ allele status, or traditional measures of cognitive and daily function.

Growing research has examined the association between plasma p-tau₁₈₁ and the clinical presentation of AD.^{11,25,27,28,29,74} Plasma p-tau₁₈₁ concentrations have been shown to correspond to AD progression²⁷ and to predict AD neuropathology irrespective of diagnosis.²⁸ Karikari et al.¹¹ found that p-tau₁₈₁ levels differentiated among NC, MCI, and AD groups in their discovery ($n = 37$), validation ($n = 989$), and primary care ($n = 105$) cohorts. The lowest concentrations were found among young adults and older individuals (> 60 years) diagnosed as NC, higher concentrations were associated with A β -positive NC and A β -negative MCI groups, and the highest concentrations were found among A β -positive MCI and AD groups. Higher plasma p-tau₁₈₁ levels have also been observed among individuals with

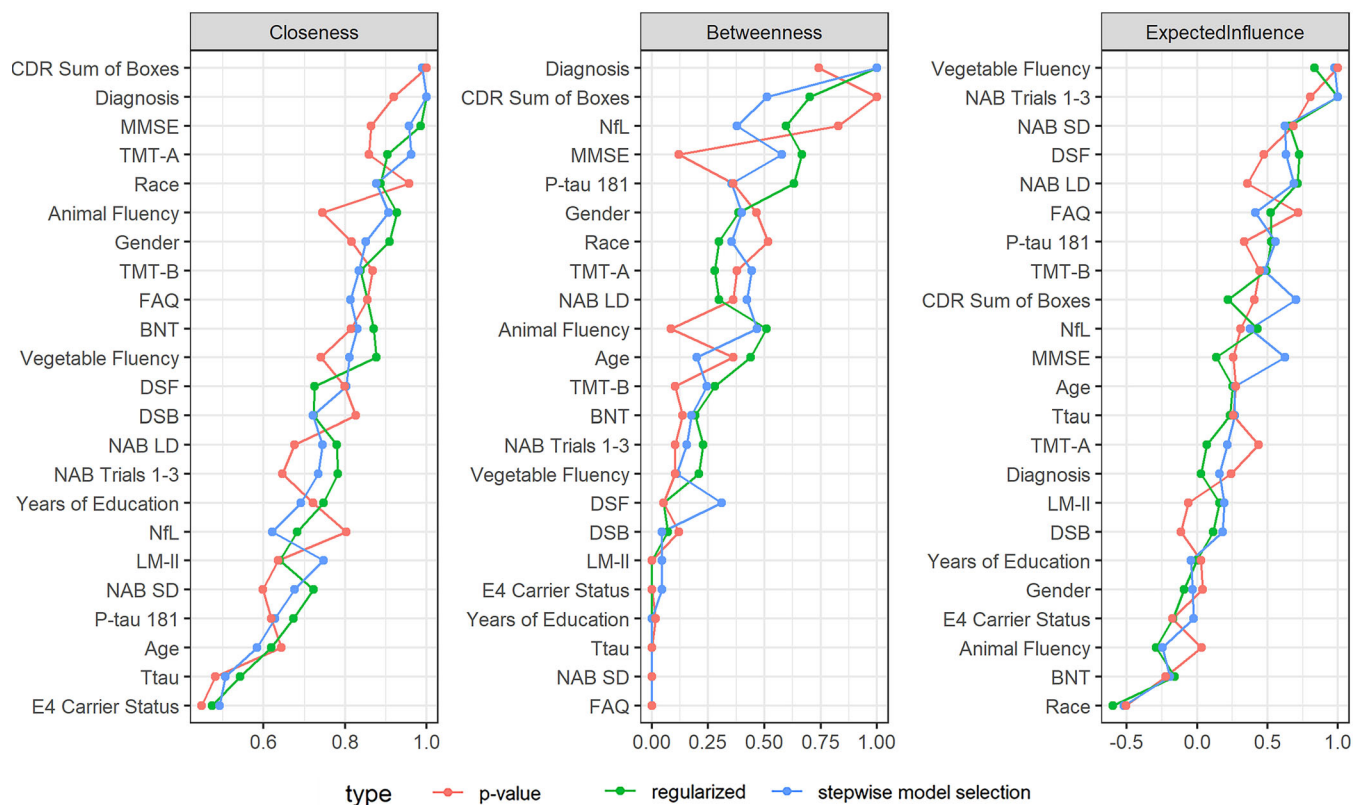


FIGURE 2 Network centrality measures with variables ranked from greatest to least. Centrality measures reflect the direct and indirect connections between nodes in a network and each node's influence in fostering connections. Closeness centrality reflects the average number of intervening nodes between a node and all other nodes. Betweenness centrality reflects how often a node fosters connections between nodes (i.e., lies on the shortest path length). Expected influence reflects the magnitude and direction of all edges connected to a node. BNT, Boston Naming Test; CDR, Clinical Dementia Rating; DSF & DSB, Digit Span Forward and Backward; FAQ, Functional Activities Questionnaire; LM-II, Logical Memory Delayed Recall; MMSE, Mini-Mental State Examination; NAB SD & LD, Neuropsychological Assessment Battery List Learning Test, Short and Long Delay; NfL, neurofilament light; P-tau₁₈₁, hyperphosphorylated tau; TMT-A & B, Trail Making Test, Parts A and B; Ttau, total tau

MCI who converted to AD dementia compared to non-converters.²⁵ In a recent study, Moscoso et al.⁷⁴ found that longitudinal increases in p-tau₁₈₁ and NfL were independently associated with cognitive decline across the AD spectrum, as well as hypometabolism and atrophy. Further, through analysis of biomarkers of neurodegeneration, as measured by MRI and fluorodeoxyglucose PET scans, they were able to differentiate the associated pattern of neurodegeneration for each plasma biomarker. Unlike plasma NfL, plasma p-tau₁₈₁ was associated with an AD-typical neurodegenerative pattern specific to A β -positive individuals.

In the present study, p-tau₁₈₁ levels were able to discriminate between individuals with AD dementia compared to NC, and were associated with neuropsychological test performance and a staging instrument of dementia severity. Although our results conflict with the aforementioned reports of p-tau₁₈₁ levels distinguishing an MCI diagnosis from NC and AD dementia,^{27,11,73} these findings (i.e., association with neuropsychological test performance, CDR score) provide some support for the use of p-tau₁₈₁ as an early prognostic biomarker for AD. Previous studies assessing p-tau₁₈₁ levels varied in their blood draw protocols, in which assays were collected from both fasting and non-fasting individuals. Björkqvist et al.³² suggested that

replication of plasma collection protocols was important for reproduction of biomarker results. Thus, our lack of findings in MCI individuals may derive from our use of a non-fasting blood draw and additional proteins interfering with the assay analysis.^{20,29}

Lack of biomarker or pathological confirmation of AD may also help to explain our lack of association with MCI. Lantero Rodriguez et al.²⁸ found that plasma p-tau₁₈₁ predicted AD neuropathology *post mortem* but did not distinguish MCI by clinical diagnosis across three time-points. Compared to dementia, MCI diagnosis is particularly heterogeneous and unstable (e.g., associated with mixed pathology and even psychiatric factors⁷⁶). Two recent studies found that plasma p-tau₁₈₁ better distinguished MCI from NC when stratified by A β status and that A β -positive individuals with MCI have similar elevations to individuals with AD dementia.^{17,77} While our MCI group had suspected AD etiology, it was not restricted to amnesic MCI and there might have been heterogeneous pathology. Finally, we focused on p-tau₁₈₁; other p-tau isotopes may be more sensitive to the early stages of AD pathology, with greater association to neocortical neurofibrillary pathology and better predictive power for conversion.⁷⁸⁻⁸⁵

In our mAUC analyses, models included plasma biomarkers (individually and in combination), analyzed with demographic variables and

APOE $\epsilon 4$ allele status. We found discrimination accuracy within the acceptable range for predicting MCI and AD dementia. The model including all three biomarkers together was the superior predictive model, which is unsurprising when attempting to measure a disease of mixed pathologies such as AD.^{22,86–88} Using plasma measures of p-tau₁₈₁, NfL, and t-tau, we were able to evaluate AD tauopathy, and non-specific neuronal injury and neurodegeneration.^{12,13,19} Plasma p-tau₁₈₁ and NfL independently strengthened the effectiveness of diagnostic prediction. However, in models with and without p-tau₁₈₁, the independent contribution of t-tau was negligible. This suggests that the cost of acquiring both t-tau and p-tau₁₈₁ might outweigh the diagnostic benefit, favoring p-tau₁₈₁ alone (i.e., adding or subtracting t-tau from various models resulted in a negligible change in overall predictive diagnostic accuracy). Our network analyses also suggested the importance of both p-tau₁₈₁ and NfL in capturing various aspects of our sample's clinical presentation (via centrality measures). Multiple plasma biomarkers will be needed to accommodate the heterogeneity and interconnectedness of AD pathology, and further research will be needed to confirm which provides optimal clinical utility.^{86,87}

Scalable and non-invasive biomarkers of AD neuropathological changes will be critical for detection and implementation of treatment efforts,^{2–8} and to meet the demands of clinical trials.⁷² Knopman et al.⁷² suggest that validated blood-based measurements would overcome economic and operational barriers for precision hypothesis testing (targeted interventions for specific disease mechanisms at optimal times in the disease course) and could improve classification and staging (a major source of trial failure). These measurements could also increase the diversity and generalizability of samples. There are concerns for how plasma biomarkers could translate to personal medicine. Largent et al.⁸⁹ proposed that a validated direct-to-consumer plasma p-tau test could benefit personal health care. However, the authors also noted that such a test could be misused if broadly available to the general population.

There are several limitations to our findings. While there is increasing support for the accuracy and reliability of plasma biomarkers for detecting AD pathology,^{3,20,27,14,77} we did not have a gold standard biomarker of AD or neurodegeneration, neither were the participants separated according to A β status. Nonetheless, our study provides a highly relevant example for the complementary use of plasma biomarkers in a primary or secondary care clinical setting in which gold standard diagnostic methods may not be feasible. The study was cross-sectional, limiting our ability to make causal inferences. Some of our findings differed from our previous analyses with this sample (e.g., the ability of t-tau to discriminate individuals with AD vs. NC at baseline; see Sugarman et al.¹⁴). These discrepancies likely resulted from the different statistical models used (i.e., multinomial models versus analysis of covariance).

Our sample and all ADRC samples are most representative of a clinic-based population (i.e., individuals who are concerned with memory problems). Thus, our results have limited generalizability to the general public. Similarly, the sample only included participants with cognitive impairment due to suspected AD. While there were few other suspected etiologies in the BU ADRC at the time of this study and

we intentionally focused on AD, AD is commonly comorbid with other neurodegenerative diseases. Limiting the sample to suspected AD may reduce the generalizability of the findings. Finally, we followed NACC UDS diagnostic criteria, which included a revision in version 3. This change in diagnostic criteria may have had some impact on our findings, albeit minimal.

5 | CONCLUSIONS

The present results suggest that plasma p-tau₁₈₁ provides unique diagnostic and clinical information and support its implementation in routine biomarker assessment related to the detection of AD dementia. The results further emphasize the importance of multiple biomarkers to capture different aspects of AD for optimal disease detection. A validated plasma biomarker panel could provide a less invasive, scalable means to transform clinical and research trials related to AD,⁷³ and perhaps personal health care.⁸⁹

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CONFLICTS OF INTEREST

AB receives royalties and consulting fees from Oxford University Press, Elsevier, and Sage Therapeutics. He has also received consulting fees from Artis Senior Living Benchmark. AM received honoraria for speaking from the Korean Society of Neuroscience, the University of Maryland, and the Texas Neurological Society. HZ has served on scientific advisory boards for Eisai, Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics, Nervgen, AZTherapies, and CogRx; has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, and Biogen; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). KB has served as a consultant, on advisory boards, or on data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. KT receives payments from the US Department of Veterans Affairs and the Alzheimer's Association. LG serves as a consultant for Rebio and Cognoptix, and has received travel expenses for HIH grant

reviews. MA serves as a consultant for Corino Therapeutics, Inc. He has received honoraria from the International Neuropsychological Society, the Allegheny General Hospital, the American Academy of Neurology, and the University of California, San Francisco. RA serves as a consultant or on scientific advisory board for Signant Health, Biogen, and GSK. RS is a member of the Mackey-White Committee of the NFL Players Association. He is a paid consultant to Biogen (Cambridge, MA, USA) and Eli Lilly (Indianapolis, IN, USA). He receives royalties for published neuropsychological tests from Psychological Assessment Resources, Inc. (Lutz, FL, USA) and is a member of the Board of Directors of King-Devick Technologies (Chicago, IL, USA). The remaining authors have nothing to disclose. The content is solely the responsibility of the authors. There is no sponsor.

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