RESEARCH ARTICLE

Scalable plasma and digital cognitive markers for diagnosis and prognosis of Alzheimer's disease and related dementias

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Abstract

INTRODUCTION: With emergence of disease-modifying therapies, efficient diagnostic pathways are critically needed to identify treatment candidates, evaluate disease severity, and support prognosis. A combination of plasma biomarkers and brief digital cognitive assessments could provide a scalable alternative to current diagnostic work-up.

METHODS: We examined the accuracy of plasma biomarkers and a 10-minute supervised tablet-based cognitive assessment (Tablet-based Cognitive Assessment Tool Brain Health Assessment [TabCAT-BHA]) in predicting amyloid β positive (Aβ+) status on positron emission tomography (PET), concurrent disease severity, and functional decline in 309 older adults with subjective cognitive impairment ($n = 49$), mild cognitive impairment ($n = 159$), and dementia ($n = 101$).

RESULTS: Combination of plasma pTau181, Aβ42/40, neurofilament light (NfL), and TabCAT-BHA was optimal for predicting Aβ-PET positivity (AUC = 0.962). Whereas NfL and TabCAT-BHA optimally predicted concurrent disease severity, combining these with pTau181 and glial fibrillary acidic protein was most accurate in predicting functional decline.

DISCUSSION: Combinations of plasma and digital cognitive markers show promise for scalable diagnosis and prognosis of ADRD.

KEYWORDS
Alzheimer's disease, blood-based biomarkers, diagnosis, digital cognitive assessment, disease monitoring

1 | BACKGROUND

The prevalence of Alzheimer's disease and related dementias (ADRD) continues to rise and is estimated to affect 153 million individuals worldwide by 2050.[1] Despite these alarming projections, the rates of missed, inaccurate, or delayed diagnoses of dementia remain high,[2,3] particularly in underserved populations, including racially and ethnically diverse individuals residing in high-income countries and those residing in low- and middle-income countries.[4] Access to timely and accurate diagnostic services remains limited,[5,6] and the need for globally scalable, accessible, and cost-effective diagnostic markers of ADRD is urgent. Implementation of such markers is also critical for establishing the infrastructure for case identification and treatment management as disease-modifying therapies become available.

Plasma biomarkers offer greater accessibility and cost effectiveness compared to the current gold standard clinical testing using cerebrospinal fluid (CSF) or positron emission tomography (PET). Among these, plasma amyloid β (Aβ), phosphorylated tau (pTau), neurofilament light (NfL) chain, and glial fibrillary acidic protein (GFAP) represent the most promising markers to date and are closest to clinical implementation.[7–9] Growing evidence supports the role of the ratio of plasma Aβ_{1-42} to Aβ_{1-40} (Aβ42/40) as a marker of cerebral Aβ pathology,[7–11] plasma pTau at threonine-181 (pTau181) or at threonine-217 (pTau217) as a marker AD-related neuropathology,[7–9,12–18] plasma NfL as an etiologically non-specific marker of neuroaxonal injury,[7–9,19,20] and plasma GFAP as a marker of reactive astrogliosis.[7–9,20,21] Given clinical and etiological heterogeneity of ADRD, a combination of different biomarkers is likely to offer greater accuracy and precision compared to any single marker, with each predictor explaining unique variance of an underlying disease process. Several studies support this premise showing that various combinations of plasma Aβ42/40, pTau, NfL, and GFAP showed highest accuracy in predicting Aβ positivity based on CSF[22,23] and PET[24] and differentiating clinical AD dementia from other neurodegenerative syndromes.[25,26] Combination of markers also exhibited highest test-retest reliability over time, which is a critical consideration for clinical implementation.[22]

Expert recommendations also highlight the importance of examining high-performing combinations of plasma and other clinical markers, particularly cognitive assessments, to maximize their diagnostic and prognostic potential.[8,9] While scarce but promising evidence to date supports complementary contributions of paper-and-pencil neuropsychological and plasma markers to predicting conversion to AD dementia,[27,28] cognitive measures that could be used in combination with plasma biomarkers in novel clinical algorithms must have characteristics that support, not hinder, widescale implementation. In particular, use of most traditional assessments (e.g., the Mini-Mental State Examination) in routine healthcare workflows has been limited by their poor sensitivity to milder stages of impairment,[29] limited validity in diverse populations,[30] and costly training, time, and administration demands.[31,32] To address these limitations, substantial progress has been made in development of sensitive and reliable digital cognitive assessments highlighting their potential as scalable and efficient clinical markers not requiring access to highly trained specialists, lengthy clinical evaluations, or complex scoring and interpretation algorithms.[31,32] Examining the combination of scalable digital cognitive and plasma markers, therefore, may provide critical insights for the development of novel efficient clinical algorithms.

This study evaluated the accuracy of a combination of plasma biomarkers (Aβ42/40, pTau181, NfL, and GFAP) and a 10-minute examiner-administered tablet-based cognitive battery (Tablet-based Cognitive Assessment Tool Brain Health Assessment, TabCAT-BHA) in predicting Aβ-PET positivity, disease severity, and functional decline. TabCAT-BHA is a brief, multidomain battery that showed excellent sensitivity to mild cognitive impairment (MCI) and typical and atypical dementias,[33–35] high reliability in tracking change over time,[34] and associations with Aβ- and tau-PET burden.[36] In accordance with the U.S. National Alzheimer's Project Act[37] to improve detection of cognitive impairment following a concern, the sample included older adult participants with subjective or objective cognitive impairment. Participants were racially and ethnically diverse individuals across diagnostic groups to support generalizability and applicability of findings in populations that have been historically excluded from ADRD biomarker research.[38]

2 | METHODS

2.1 | Participants

The study was approved by the University of California San Francisco (UCSF) Committee on Human Research. All participants provided written informed consent. Participants were adults aged 50 or older enrolled in longitudinal observational studies at the UCSF Memory and

Aging Center, who were clinically characterized as having subjective cognitive impairment (SCI) or met criteria for MCI or dementia. All participants underwent a comprehensive diagnostic evaluation consisting of neurological examination, multidomain neuropsychological testing, clinical interview with an informant including Clinical Dementia Rating Scale (CDR),[39] and structural neuroimaging. Clinical diagnoses were made in multidisciplinary consensus conferences based on published criteria as previously described.[12,33,34]

The SCI group ($n = 49$) included older adults who endorsed worsening of their memory or other thinking abilities on clinical interview, but performed within normal limits on neurological evaluation, neuropsychological testing, and CDR. Among 159 participants with MCI, 72 (45%) were characterized with an AD spectrum clinical syndrome, including 58 with a multidomain amnestic syndrome,[40] 10 with logopenic variant of primary progressive aphasia (lvPPA),[41] and 4 with posterior cortical atrophy (PCA).[42] The remaining participants with MCI were clinically diagnosed with a non-AD spectrum syndromes, including non-amnestic MCI ($n = 56$), corticobasal syndrome (CBS, $n = 4$),[43] non-fluent variant of primary progressive aphasia (nfvPPA, $n = 16$),[41] progressive supranuclear palsy (PSP, $n = 4$),[44] semantic variant of primary progressive aphasia (svPPA, $n = 5$),[41] and traumatic encephalopathy syndrome (TES, $n = 2$).[45] Among 101 participants with dementia, 48 (48%) were clinically diagnosed with an AD spectrum syndrome, including 41 with AD amnestic dementia,[46] 5 with lvPPA,[41] and 2 with PCA.[42] The remaining participants were diagnosed with behavioral variant frontotemporal dementia ($n = 31$),[47] CBS ($n = 3$),[43] dementia with Lewy bodies ($n = 4$),[48] nfvPPA ($n = 2$),[41] PSP ($n = 6$),[44] svPPA ($n = 6$),[41] and TES ($n = 1$).[45]

All participants completed a blood draw and TabCAT-BHA at baseline independent of standard diagnostic procedures. The average time difference between a blood draw and TabCAT-BHA completion was 2.3 ± 7.7 days. We only included participants whose plasma biomarker measurements were successful. Additional exclusion criteria were presence of severe psychiatric illness, known non-neurodegenerative neurological condition affecting cognition, or significant substance use disorder and/or systemic illness. Longitudinal disease severity data were available in a subsample of 32 SCI, 107 MCI, 46 dementia participants who completed the CDR at baseline and annual follow-up visits ($n = 185$ with 2 visits; $n = 88$ with 3 visits; $n = 38$ with 4 or more visits). Average time between visits was 1.3 ± 0.6 years.

2.2 | Measures and procedures

2.2.1 | TabCAT-BHA

TabCAT-BHA is a 10-min cognitive battery programmed in the Tab-CAT software platform (UCSF, San Francisco, CA). It is comprised of 2 required subtests: Favorites (associative memory) and Match (executive functioning and processing speed); and 2 optional subtests: Line Orientation (visuospatial) and Animal Fluency (language).[33–35] Detailed task descriptions are available at memory.ucsf.edu/tabcat

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature on plasma biomarkers for diagnosis and prognosis of Alzheimer's disease and related dementias using traditional sources (e.g., PubMed). Supplementing plasma biomarkers with cognitive and other clinical tools offers greater accuracy, and there are ongoing efforts to examine high performing combinations of different markers to maximize diagnostic precision.

2. **Interpretation**: Our findings show that a combination of plasma and digital cognitive markers is highly accurate at predicting amyloid β-positron emission tomography (Aβ-PET) positivity, concurrent disease severity, and longitudinal functional decline.

3. **Future directions**: Replication of the results in more representative and socioeconomically diverse communities is needed to support future clinical implementation of these markers.

and were described previously.[33,34] All participants completed the TabCAT-BHA on a 9.7-inch iPad with a trained examiner in a private examination room. Performance on the TabCAT-BHA battery was included in all analyses in the form of a previously validated cognitive composite score,[34] which is based on the demographically adjusted (age, sex, education, testing language) Favorites and Match scores.

2.2.2 | Plasma biomarker measurements

Blood samples were obtained by venipuncture in ethylenediaminetetraacetic acid (EDTA) tubes for plasma as previously described.[12] After centrifugation at 2000 g for 10 min at 4°C, plasma samples were aliquoted in polypropylene tubes and stored at −80°C, with an average needle-to-freezer time <2 h. Before analysis, samples underwent only one freeze-thaw cycle. Biomarker concentrations were measured in duplicate using commercially available pTau181 V2 (pTau181; lot #503008) and Neurology 4-PLEX E (Aβ40, Aβ42, NfL, and GFAP; lot #503105) Quanterix kits (Billerica, MA) on the Simoa HD-X platform at UCSF. For each kit 100 microliters of plasma were diluted 1:4 by the instrument. The instrument operator was blinded to clinical variables. For pTau181, all samples were measured above the kit lower limit of quantification (LLOQ) of 0.085 pg mL^{-1} with the mean coefficient of variation (CV) of 7.3%. For Aβ40 and Aβ42, all samples were measured above the LLOQ of 1.02 pg mL^{-1} and 0.378 pg mL^{-1} (respectively) with the average CVs of 3.3% and 3.4% (respectively). For NfL and GFAP, all samples were measured above the LLOQ of 0.400 pg mL^{-1} and 2.89 pg mL^{-1} (respectively) with the mean CVs of 5.3% and 6.3% (respectively).

2.2.3 | Aβ-PET acquisition and processing

Aβ-PET was performed independent of diagnostic procedures in a subset of 105 participants, including 6 with SCI, 64 with MCI (36 with AD spectrum, 28 with a non-AD spectrum), and 35 with dementia (19 with AD spectrum, 16 with a non-AD spectrum). Aβ-PET acquired with 11C-Pittsburgh Compound B (PIB, n = 82), 18F-Florbetapir (n = 22), or 18F-Florbetaben (n = 1) radiotracers. The average time between plasma sample collection and PET imaging was 136 ± 256 days. PET scans were acquired in list mode on PET-CT scanners (GE Discovery VCT, n = 22; Siemens Biograph 6 Truepoint, n = 83) using standard acquisition protocols: 50-70 min acquisition for Florbetapir and PIB and 90-110 min post injection for Florbetaben. PET data were attenuation corrected using low dose CT and reconstructed as four five-minute frames using an ordered subset expectation maximization algorithm. PET frames were realigned to the first one and averaged; this mean PET image was used to perform a visual read by a trained clinician following FDA-approved guidelines for Florbetaben and Florbetapir, or internal reading guidelines for PIB (see[49,50] for validation of the PIB-PET visual read approach in PET-to-autopsy studies).

2.2.4 | Apolipoprotein E genotyping

Apolipoprotein E (APOE) genotyping was performed in 302 (98%) participants (48 SCI, 155 MCI, 99 dementia) and was based on DNA analysis from peripheral blood samples as described previously[51] APOE ε4 status was coded as "1" for homozygotes and heterozygotes of ε4 and as "0" otherwise. There were eight participants with a ε2/ε4 genotype in the whole sample, whose APOE data were not used in the analyses.

2.3 | Statistical analyses

Baseline group differences were determined using analyses of variance (ANOVA) for continuous variables and Fisher's exact tests for categorical variables. Pairwise comparisons were performed using the Bonferroni method. Values of raw concentrations of plasma pTau181 (skewness = 1.2, kurtosis = 1.4), NfL (skewness = 5.0, kurtosis = 36.2), and GFAP (skewness = 2.0, kurtosis = 5.6) were not normally distributed and were natural log-transformed for baseline ANOVA and linear regression analyses. The distribution of Aβ42/40 ratio was within expectations for a normal distribution (skewness = 0.01, kurtosis = 0.34). Transformed values approximated normal distributions for each biomarker, including log-transformed pTau181 (skewness = 0.0, kurtosis = −0.5), log-transformed NfL (skewness = 0.6, kurtosis = 1.3), and log-transformed GFAP (skewness = 0.2, kurtosis = −0.1).

We performed logistic regression models with receiver operating characteristic (ROC) curves to determine the accuracy of plasma biomarkers and TabCAT-BHA in differentiating Aβ-PET status at baseline. Individual models were run for each of the markers and the full model was comprised of all markers included simultaneously. Model selection was performed using the information-theoretic approach based on the Akaike information criterion (AIC).[27,52] The optimal model was defined as having the lowest AIC and was considered to maximize the optimal trade-off between model fit and sparsity.[52] Differences between areas under the ROC curves (AUC) were examined using DeLong tests. All models were performed with and without covariates for age (years), sex (coded as "1" for female and "0" for male), education (years), APOE ε4 status (coded as "1" for presence of one or two ε4 alleles and "0" for absence of an ε4 allele), and time difference between PET acquisition and plasma collection (days).

Multiple linear regression models were used to examine baseline associations of plasma and TabCAT-BHA markers with disease severity measured by the CDR Sum of Boxes score (CDR-SB). All variables were included simultaneously, and unstandardized coefficients were reported. Linear mixed effect models with random intercepts and slopes were used to examine the associations between baseline values of plasma and TabCAT-BHA markers with longitudinal changes on the CDR-SB (number of visits: mean = 2.62, SD = 0.85). All models controlled for age, sex, education, and APOE ε4 status; longitudinal analyses additionally controlled for time since baseline visit (years) and baseline clinical diagnosis. To account for phenotypic heterogeneity, we additionally repeated both baseline and longitudinal models in AD spectrum and FTLD spectrum clinical groups separately using CDR plus the National Alzheimer's Coordinating Center FTLD rating (CDR+NACC/FTLD) Sum of Boxes as an outcome.[53]

All analyses were performed in R (v 4.2.3, R Project for Statistical Computing) with two-tailed significance level set at P < 0.05. Linear models were checked for overdispersion, influential values, and multicollinearity. We report P values without adjusting for multiple comparisons as this methodology focuses on avoiding one or more results with P < 0.05 in the case where all differences are truly zero, which represents an unlikely hypothesis in our analyses. Therefore, we use scientific judgment rather than formal methods of adjustment to indicate where caution is warranted despite findings with P < 0.05.

3 | RESULTS

3.1 | Baseline differences

The study cohort was comprised of 309 older adults, including 49 participants with SCI, 159 with MCI, and 101 with dementia. Baseline demographic and clinical characteristics, plasma biomarker levels, and TabCAT-BHA performance are reported in Table 1. Among 260 participants with MCI and dementia, 120 (46%) were diagnosed with an AD spectrum clinical syndrome, 77 (30%) with an FTLD spectrum syndrome, and 63 (24%) with other clinical syndromes (detailed description is provided in Methods). The SCI, MCI, and dementia groups did not significantly differ with regard to age, sex, APOE ε4 status, and AD spectrum clinical phenotype (Table 1). Participants in the SCI group had more years of education compared to the MCI group

TABLE 1 Baseline demographic and clinical characteristics and biomarker values.

	SCI (n = 49)	MCI (n = 159)	Dementia (n = 101)	P-Value
Age (years), M (SD)	68.9 (9.3)	68.2 (9.3)	67.4 (9.9)	0.623
Sex (female), n (%)	26 (53%)	82 (52%)	43 (43%)	0.311
Education (years), M (SD)	16.4 (3.6)	14.8 (4.0)	15.2 (3.0)	0.033
Race/ethnicity				0.001
Asian, n (%)	12 (24%)	21 (13%)	8 (8%)	
Non-Hispanic Black, n (%)	2 (4%)	6 (4%)	3 (3%)	
Hispanic, n (%)	13 (27%)	25 (16%)	12 (12%)	
Non-Hispanic White, n (%)	22 (45%)	107 (67%)	78 (77%)	
APOE e4 allele, n/total n (%)	13/46 (28%)	49/152 (32%)	34/96 (35%)	0.697
AD spectrum syndrome, n (%)	–	72 (45%)	48 (48%)	0.799
No. of longitudinal visits, M (SD)	2.8 (0.9)	2.6 (0.8)	2.3 (0.5)	<0.001
Years since baseline (longitudinal visits only), M (SD)	2.7 (1.6)	1.9 (1.1)	1.4 (0.7)	<0.001
CDR-SB, M (SD)	0.26 (0.53)	2.04 (1.42)	5.89 (2.29)	<0.001
Plasma Aβ42/40 (pg ml^{-1}), M (SD)	0.07 (0.01)	0.07 (0.01)	0.06 (0.01)	0.029
Plasma pTau181 (pg ml^{-1}), M (SD)	1.57 (0.69)	2.03 (1.05)	2.47 (1.41)	<0.001*
Plasma NfL (pg ml^{-1}), M (SD)	23.59 (12.97)	29.67 (24.77)	42.36 (39.15)	<0.001*
Plasma GFAP (pg ml^{-1}), M (SD)	126.52 (56.04)	163.93 (106.54)	206.59 (125.68)	<0.001*
TabCAT-BHA Cognitive Composite, M (SD)	−0.71 (1.19)	−2.30 (1.74)	−3.99 (1.95)	<0.001

Note: Group differences were examined using analyses of variance for continuous outcomes and Fisher's exact tests for categorical outcomes.
Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; CDR-SB, Clinical Dementia Rating Scale Sum of Boxes; M, mean; MCI, mild cognitive impairment; NfL, neurofilament light; SCI, subjective cognitive impairment; SD, standard deviation; TabCAT-BHA, Tablet-based Cognitive Assessment Tool Brain Health Assessment.
*P-values are based on natural log-transformed plasma pTau181, NfL, and GFAP values.

and included fewer individuals who identified as non-Hispanic White compared to the MCI and dementia groups (Table 1).

As shown in Table 1, post hoc pairwise comparisons revealed that plasma Aβ42/40 concentrations were higher in participants with dementia compared to those with MCI (P = 0.025) but not SCI (P = 0.222). Concentrations of plasma pTau181 were significantly different across groups with highest levels in participants with dementia (P vs. MCI = 0.034; P vs. SCI < 0.001) followed by those with MCI (P vs. SCI = 0.043). Plasma NfL was elevated in dementia when compared to MCI (P < 0.001) and SCI (P < 0.001); differences between MCI and SCI groups were not significant (P = 0.242). Similarly, plasma GFAP was higher in dementia participants compared to MCI (P = 0.002) and SCI (P < 0.001) with no significant differences between MCI and SCI groups (P = 0.094). Performance on the TabCAT-BHA was significantly different across diagnostic groups with worst performance in participants with dementia (P vs. MCI < 0.001; P vs. SCI < 0.001) followed by MCI (P vs. SCI < 0.001).

3.2 | Associations with Aβ-PET at baseline

In a subset of 105 participants who completed Aβ-PET (6 SCI, 64 MCI, 35 dementia), 58 (55%) were classified as Aβ positive based on

expert visual read,[49,50] including 4/6 participants with SCI, 34/64 with MCI, and 20/35 with dementia. In individual models without covariates, plasma pTau181 had the highest AUC to differentiate Aβ+ vs. Aβ- in the total sample (n = 105; AUC = 0.895, 95% confidence interval [CI]: 0.832-0.959) and SCI and MCI groups only (n = 70; AUC = 0.888, 95% CI: 0.808-0.967). Inclusion of covariates for age, female sex, education, APOE ε4 status, and time difference between PET acquisition and plasma collection improved discrimination for each of the markers (Table 2) with plasma pTau181 again exhibiting the highest AUC in the total sample (n = 101; AUC = 0.933, 95% CI: 0.885-0.980) and in SCI and MCI groups only (n = 67; AUC = 0.939, 95% CI: 0.883-0.995). Findings on the performance of individual plasma and TabCAT-BHA markers in discriminating Aβ-PET status without and with covariates are presented in Table 2.

In a combined model, in which all markers were included simultaneously with demographic and clinical covariates, plasma Aβ42/40, pTau181, NfL, and TabCAT-BHA cognitive composite were the only significant predictors of Aβ-PET positivity in the total sample with an AUC of 0.971 (95% CI: 0.944-0.997, Table 3). The optimal model offering the best trade-off between model fit and sparsity based on the AIC included plasma Aβ42/40, pTau181, NfL, TabCAT-BHA, and age (Table 3). Discrimination accuracy of the optimal model (AUC = 0.964, 95% CI: 0.936-0.993) was significantly better compared

TABLE 2 Accuracy of individual plasma biomarkers and TabCAT-BHA in discriminating Aβ-PET status.

	AUC (95% CI)	SN	SP	PPV	NPV
Total sample without covariates (47 Aβ-PET negative vs. **58 Aβ-PET positive)**					
Aβ42/40	0.750 (0.655–0.845)	0.690	0.766	0.784	0.667
pTau181	0.895 (0.832–0.959)	0.879	0.809	0.850	0.844
NfL	0.493 (0.367–0.619)	0.931	0.319	0.628	0.789
GFAP	0.772 (0.678–0.866)	0.862	0.596	0.725	0.778
TabCAT-BHA	0.700 (0.602–0.799)	0.345	1.000	1.000	0.553
Total sample with covariates[a] (45 Aβ-PET negative vs. **56 Aβ-PET positive)**					
Aβ42/40	0.886 (0.824–0.948)	0.679	0.933	0.927	0.700
pTau181	0.933 (0.885–0.980)	0.804	0.933	0.938	0.792
NfL	0.864 (0.793–0.935)	0.786	0.822	0.846	0.755
GFAP	0.895 (0.835–0.956)	0.875	0.778	0.831	0.833
TabCAT-BHA	0.918 (0.866–0.971)	0.893	0.844	0.877	0.864
SCI and MCI only without covariates (32 Aβ-PET negative vs. **38 Aβ-PET positive)**					
Aβ42/40	0.790 (0.683–0.898)	0.711	0.813	0.818	0.703
pTau181	0.888 (0.808–0.967)	0.921	0.750	0.814	0.889
NfL	0.527 (0.373–0.681)	0.921	0.344	0.625	0.786
GFAP	0.772 (0.659–0.886)	0.789	0.656	0.732	0.724
TabCAT-BHA	0.642 (0.513–0.772)	0.474	0.781	0.720	0.556
SCI and MCI only with covariates[a] (31 Aβ-PET negative vs. **36 Aβ-PET positive)**					
Aβ42/40	0.927 (0.867–0.986)	0.806	0.935	0.935	0.806
pTau181	0.939 (0.883–0.995)	0.806	0.968	0.967	0.811
NfL	0.883 (0.798–0.967)	0.889	0.774	0.821	0.857
GFAP	0.913 (0.843–0.983)	0.889	0.839	0.865	0.867
TabCAT-BHA	0.883 (0.805–0.960)	0.667	0.935	0.923	0.707

Abbreviations: Aβ-PET, amyloid β positron emission tomography; APOE, apolipoprotein E; AUC, area under the ROC curve; GFAP, glial fibrillary acidic protein; MCI, mild cognitive impairment; NfL, neurofilament light; NPV, negative predictive value; PPV, positive predictive value; SCI, subjective cognitive impairment; SN, sensitivity; SP, specificity; TabCAT-BHA, Tablet-based Cognitive Assessment Tool Brain Health Assessment.

[a]Covariates include age (years), sex (female), education (years), presence of APOE ε4 allele (binary), and time difference between PET acquisition and plasma collection (days).

to the reduced models including plasma pTau181, TabCAT-BHA, and age (AUC = 0.919, 95% CI: 0.868-0.970; P vs. optimal model = 0.023) and plasma pTau181 and age only (AUC = 0.897, 95%CI: 0.833-0.960; P vs. optimal model = 0.011) using Delong tests. Performance of combined models is presented in Figure 1.

3.3 | Associations among markers and disease severity at baseline

Plasma biomarkers were significantly correlated with each other with magnitudes of associations ranging from weak (Aβ42/40 with NfL, $\rho = -0.169$, $P = 0.003$) to strong (NfL with GFAP, $\rho = -0.575$, $P < 0.001$). TabCAT-BHA cognitive composite showed moderate correlations with plasma GFAP ($\rho = -0.307$, $P < 0.001$) and weaker correlations with plasma Aβ42/40 ($\rho = 0.196$, $P < 0.001$), pTau181 ($\rho = -0.271$, $P < 0.001$), and NfL ($\rho = -0.211$, $P < 0.001$). Bivariate cor-

relations among all scalable markers by diagnostic group are reported in Supplementary Table 1.

We performed individual multiple linear regression models to examine baseline associations between each of the scalable markers with Clinical Dementia Rating (CDR) Sum of Boxes. All markers were individually associated with disease severity when covarying for age, female sex, education, and presence of at least one APOE ε4 allele, including Aβ42/40 ($\beta = -32.231$, $P = 0.005$), pTau181 ($\beta = 0.956$, $P = 0.002$), NfL ($\beta = 1.306$, $P < 0.001$), GFAP ($\beta = 1.479$, $P < 0.001$), and TabCAT-BHA ($\beta = -0.719$, $P < 0.001$). The results are illustrated in Figure 2.

In a linear model including all scalable markers as predictors simultaneously, only log-transformed plasma NfL ($\beta = 0.625$, $P = 0.034$), TabCAT-BHA ($\beta = -0.688$, $P < 0.001$), and female sex ($\beta = -0.676$, $P = 0.013$) were significantly associated with disease severity at baseline (detailed output is reported in Supplementary Table 2). A reduced model including log-transformed plasma NfL, TabCAT-BHA,

TABLE 3 Results of logistic regression analyses including baseline values of scalable plasma and TabCAT-BHA markers as predictors, demographic and clinical covariates, and Aβ-PET status as an outcome (n = 105; 47 Aβ-PET negative, 58 Aβ-PET positive).

	β	SE	P-Value
Full model (AIC = 61)			
Plasma Aβ42/40	−94.009	47.496	0.048
Plasma pTau181	2.202	0.714	0.002
Plasma NfL	−0.081	0.034	0.017
Plasma GFAP	0.001	0.006	0.886
TabCAT-BHA	−0.827	0.368	0.025
Age (years)	0.132	0.068	0.050
Sex (female)	−0.290	1.033	0.779
Education (years)	0.117	0.239	0.625
APOE ε4 allele	2.138	1.285	0.096
PET/Plasma time difference (days)	0.005	0.003	0.103
Optimal model (AIC = 63)			
Plasma Aβ42/40	−94.597	34.328	0.006
Plasma pTau181	2.435	0.559	<0.001
Plasma NfL	−0.088	0.031	0.005
TabCAT-BHA	−0.619	0.258	0.016
Age (years)	0.079	0.046	0.085
pTau181, TabCAT-BHA, age (AIC = 84)			
Plasma pTau181	1.977	0.432	<0.001
TabCAT-BHA	−0.525	0.195	0.007
Age (years)	0.054	0.037	0.139
pTau181, age (AIC = 92)			
Plasma pTau181	2.091	0.407	<0.001
Age (years)	0.019	0.031	0.527

Abbreviations: Aβ-PET, amyloid β positron emission tomography; AIC, Akaike information criterion; APOE, apolipoprotein E; GFAP, glial fibrillary acidic protein; NfL, neurofilament light; PET, positron emission tomography; SE, standard error; TabCAT-BHA, Tablet-based Cognitive Assessment Tool Brain Health Assessment.

and female sex as the only predictors did not result in a significantly worse model fit using likelihood ratio testing (χ^2 = 2.377, P = 0.795).

3.4 | Associations with changes in disease severity

In separate linear mixed effect models for each of the scalable markers, elevated baseline plasma pTau181 (β = 0.510, P < 0.001) and NfL (β = 0.021, P < 0.001) were associated with greater longitudinal increases on the CDR Sum of Boxes. Lower baseline TabCAT-BHA cognitive composite values were associated with greater increases in disease severity (β = −0.389, P < 0.001). In contrast, neither baseline values of plasma Aβ42/40 (β = −4.490, P = 0.575) nor plasma GFAP (β = 0.0002, P = 0.829) were significantly associated with changes in

CDR Sum of Boxes over time. Detailed outputs of each of the models are reported in Supplementary Tables 3-7.

In a combined mixed model, in which baseline values of all scalable markers were included as predictors simultaneously along with demographic and clinical covariates, higher baseline plasma pTau181 (β = 0.357, P < 0.001) and NfL (β = 0.018, P < 0.001) and lower baseline GFAP (β = −0.002, P = 0.029) and TabCAT-BHA (β = −0.320, P < 0.001) were independently associated with longitudinal increases in disease severity (Figure 3). Full model output of the combined model is presented in Table 4. Based on the analysis of marginal coefficients of determination for mixed models,[54] total variance explained by the combined effects of plasma pTau181, NfL, GFAP, and TabCAT-BHA was 29% after accounting for fixed effects of age, sex, education, APOE ε4 status, and baseline diagnosis.

3.5 | Additional analyses

To account for phenotypic heterogeneity in our sample, we performed separate models examining cross-sectional and longitudinal associations between a combination of scalable markers with disease severity in AD spectrum and FTLD spectrum subgroups using the CDR+NACC/FTLD[53] Sum of Boxes score as an outcome. In 120 participants with AD spectrum clinical syndromes (72 MCI, 48 dementia), TabCAT-BHA (β = −1.346, P < 0.001), and female sex (β = −2.112, P = 0.027) were the only markers associated with CDR+NACC/FTLD Sum of Boxes score cross-sectionally. In 77 individuals with FTLD spectrum diagnoses (29 MCI, 48 dementia), only TabCAT-BHA (β = −1.341, P = 0.002) was significantly associated with the baseline CDR+NACC/FTLD, with plasma Aβ42/40 ratio approaching significance (β = −116.093, P = 0.062). The detailed results of cross-sectional multiple regression models in AD and FTLD subgroups are presented in Supplementary Table 8.

Baseline plasma pTau181 (β = 0.536, P < 0.001), NfL (β = 0.015, P = 0.007), and TabCAT-BHA (β = −0.299, P < 0.001) were significantly associated with longitudinal changes in CDR+NACC/FTLD in linear mixed models with all scalable markers and demographic and clinical variables included as predictors simultaneously in a subsample of participants with AD syndromes (n = 78; 51 MCI, 27 dementia). In the FTLD subsample (n = 33; 15 MCI, 18 dementia), only baseline TabCAT-BHA (β = −0.572, P = 0.007) was significantly associated with longitudinal increases in the CDR+NACC/FTLD, with baseline plasma NfL (β = 0.039, P = 0.075) approaching significance. Detailed results from these models are reported in Supplementary Table 9.

4 | DISCUSSION

This study examined the performance of a combination of scalable plasma biomarkers and brief digital cognitive battery TabCAT-BHA in relation to ADRD diagnostic outcomes. Specifically, we investigated how well a combination of these markers was able to detect in vivo Aβ pathology on PET, reflect disease staging at baseline, and predict
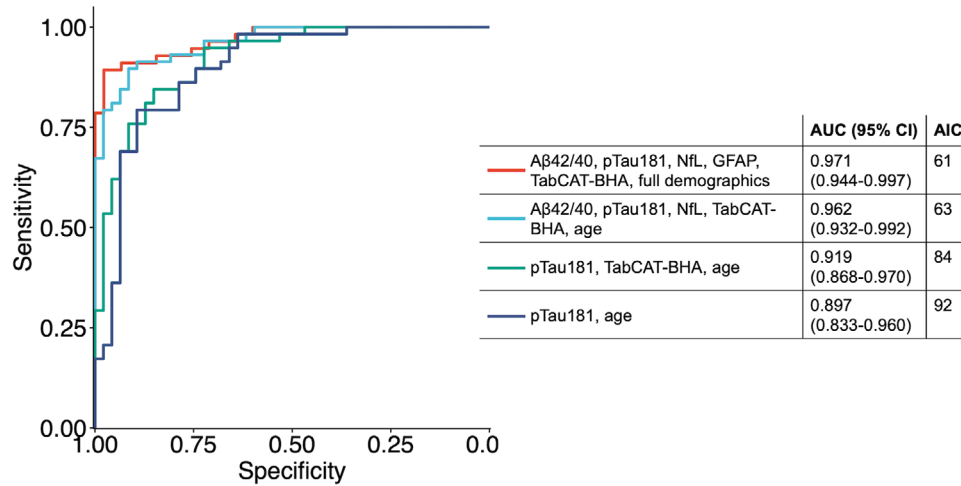
FIGURE 1 Comparative performance of models combining plasma biomarkers, TabCAT-BHA, and demographic and clinical covariates in discriminating Aβ-PET status. ROC curves are based on logistic regression models in 105 participants (47 Aβ-PET negative, 58 Aβ-PET positive). Full model (red) included all markers and demographic variables (age, sex, education, presence of APOE ε4 allele, and time difference between PET acquisition and plasma collection) as predictors. Optimal model (teal) offered the best fit with lowest number of predictors. Aβ-PET, amyloid β positron emission tomography; AIC, Akaike information criterion; APOE, apolipoprotein E; AUC, area under the ROC curve; CI, confidence interval; ROC, receiver operating characteristic; TabCAT-BHA, Tablet-based Cognitive Assessment Tool Brain Health Assessment.
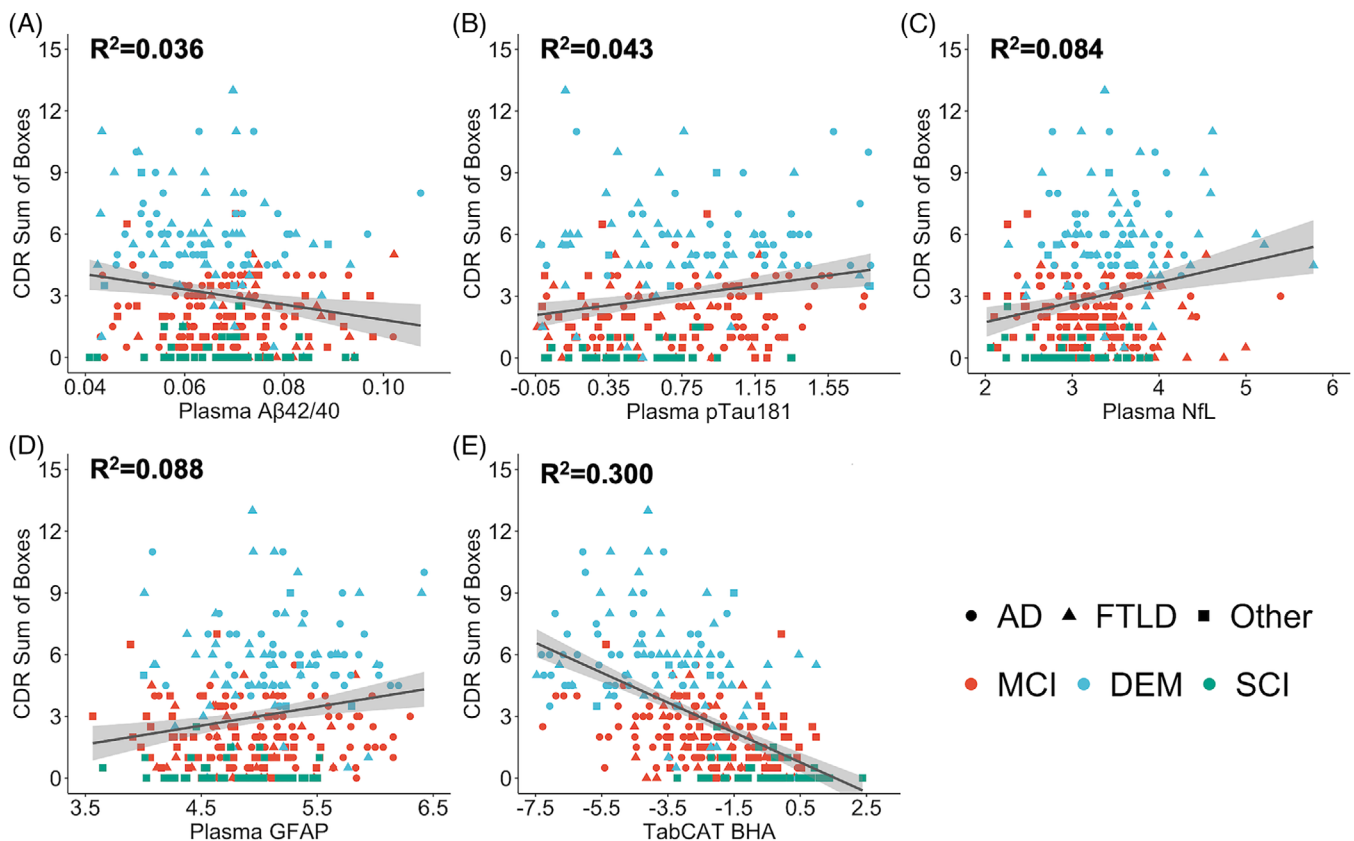

FIGURE 2 Baseline associations between plasma Aβ42/40 (A), pTau181 (B), NfL (C), GFAP (D), and TabCAT-BHA cognitive composite (E) with the Clinical Dementia Rating Scale (CDR) Sum of Boxes score. Coefficients of determination are based on multiple linear models covarying for age, female sex, education, and presence of an APOE ε4 allele. Raw values of plasma pTau181, NfL, and GFAP concentrations were natural log-transformed. Shapes represent clinical syndrome groups (circles = Alzheimer's disease spectrum, triangles = frontotemporal lobar degeneration spectrum, squares = other neurodegenerative syndromes) and colors represent diagnosis groups (red = mild cognitive impairment, teal = dementia, green = subjective cognitive impairment). Aβ, amyloid β; APOE, apolipoprotein E; GFAP, glial fibrillary acidic protein; NfL, neurofilament light; TabCAT-BHA, Tablet-based Cognitive Assessment Tool Brain Health Assessment.
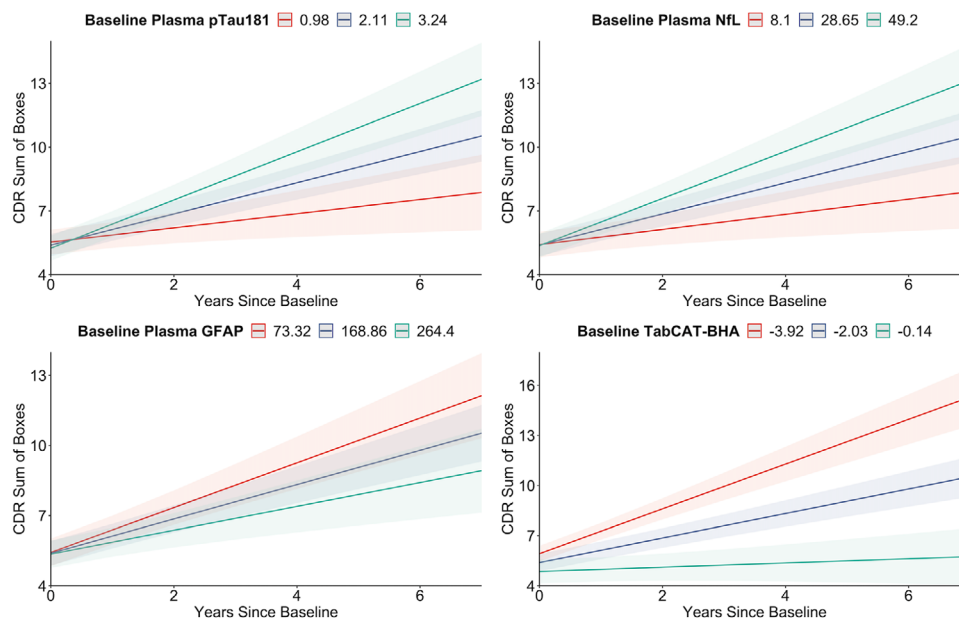
FIGURE 3 Modeled associations of baseline values of plasma pTau181, NfL, GFAP, and TabCAT-BHA with longitudinal changes on the Clinical Dementia Rating (CDR) Sum of Boxes score. Regression lines are based on the results of linear mixed effect models with random intercepts and slopes in which all markers were simultaneously included as predictors covarying for age, sex, education, presence of APOE ε4 allele, baseline diagnostic group, and years since baseline. Colors represent values one standard deviation below the mean predictor value (red lines), the mean predictor value (blue lines), and one standard deviation above the mean predictor value (green lines). APOE, apolipoprotein E; GFAP, glial fibrillary acidic protein; NfL, neurofilament light; TabCAT-BHA, Tablet-based Cognitive Assessment Tool Brain Health Assessment.

TABLE 4 Results of linear mixed model analyses including baseline values of all scalable plasma and TabCAT-BHA markers as predictors, demographic and clinical covariates, and Clinical Dementia Rating Scale (CDR) Sum of Boxes as an outcome ($n = 185$; 32 SCI, 107 MCI, 46 dementia).

	β	SE	df	P
Baseline plasma Aβ42/40 x Years since baseline	2.060	5.937	99	0.729
Baseline plasma pTau181 x Years since baseline	0.357	0.082	103	<0.001
Baseline plasma NfL x Years since baseline	0.018	0.004	90	<0.001
Baseline plasma GFAP x Years since baseline	−0.002	0.001	125	0.029
Baseline TabCAT-BHA x Years since baseline	−0.320	0.047	120	<0.001
Baseline plasma Aβ42/40	−0.122	8.433	159	0.149
Baseline plasma pTau181	−0.128	0.117	162	0.274
Baseline plasma NfL	−0.001	0.006	157	0.876
Baseline plasma GFAP	−0.001	0.001	165	0.658
Baseline TabCAT-BHA	−0.283	0.081	166	<0.001
Age (years; centered)	0.012	0.014	163	0.397
Sex (female)	0.163	0.228	164	0.476
Education (years)	0.025	0.037	165	0.500
APOE ε4 allele	0.209	0.251	166	0.408
Baseline dementia diagnosis (reference)	–	–	–	–
Baseline MCI diagnosis	−3.487	0.302	165	<0.001
Baseline SCI diagnosis	−4.832	0.431	164	<0.001
Years since baseline	−0.940	0.477	96	0.052

Abbreviations: Aβ, amyloid β; APOE, apolipoprotein E; df, degrees of freedom; GFAP, glial fibrillary acidic protein; MCI, mild cognitive impairment; NfL, neurofilament light; SCI, subjective cognitive impairment; SE, standard error; TabCAT-BHA, Tablet-based Cognitive Assessment Tool Brain Health Assessment. Degrees of freedom are estimated using Satterthwaite's method.

future changes in disease severity. When each biomarker and TabCAT-BHA were examined individually, pTau181 showed the best accuracy in detecting Aβ-PET positivity particularly when combined with demographic and clinical information, including age, sex, education, and APOE ε4 status (AUC = 0.933, 95% CI: 0.885-0.980, Table 2). While these findings are largely consistent with prior reports on the performance of plasma pTau181 in clinical cohorts,[12–14] we found that combining TabCAT-BHA with demographics and clinical data enhanced accuracy at discriminating Aβ status (AUC = 0.918, 95% CI: 0.866-0.971, Table 2). When all markers were analyzed simultaneously, a combination of age with plasma Aβ42/40, pTau181, NfL, and TabCAT-BHA had the highest accuracy against Aβ-PET with an AUC of 0.962 (95% CI: 0.932-0.992) within an optimal model selection paradigm (Figure 1). These results provide further support for superior performance of combinations compared to any single one of the included plasma biomarkers in relation to gold standard anchors[22–26] and constitute strong evidence for inclusion of scalable cognitive markers into future algorithms.

The added value of efficient cognitive assessment was most evident across findings related to disease severity outcomes. Although each of the scalable markers was associated with CDR Sum of Boxes score at baseline, TabCAT-BHA cognitive composite showed the strongest magnitude of the association (Figure 2). When all markers were included simultaneously, only TabCAT-BHA and plasma NfL were cross-sectionally associated with disease severity (Supplementary Table 2), which is unsurprising given prior evidence of high sensitivity of these two markers to tracking disease severity.[33,55,56] While our findings are generally consistent with previously reported baseline associations between pTau181 and CDR Sum of Boxes,[12] these relationships were no longer significant when pTau181 was included with TabCAT-BHA and plasma NfL in our sample (Supplementary Table 2). These results have important implications for clinical implementation algorithms and suggest that scalable plasma and digital cognitive markers play complementary roles for supporting ADRD diagnosis.

In our sample, baseline plasma pTau181, NfL, GFAP, and TabCAT-BHA were significant predictors of future functional decline and increases in disease severity across SCI, MCI, and dementia groups (Table 4, Figure 3). Despite limited sample sizes, these results were mostly replicated in participants with AD spectrum clinical syndromes, aside from loss of significance for plasma GFAP (Supplementary Table 9). In a smaller subsample with FTLD clinical syndromes, only baseline TabCAT-BHA reached significance while plasma NfL was trending (Supplementary Table 9). These results complement prior studies showing that the combination of plasma pTau and cognitive tests predicted conversion from SCI and MCI to AD dementia[27,28] and extend current knowledge by examining a broader combination of markers in a highly clinically heterogeneous cohort. The relationships between baseline plasma pTau181, NfL, and TabCAT-BHA with longitudinal changes in CDR were in expected directions with higher baseline pTau181 and NfL and lower baseline TabCAT-BHA predicting faster rates of decline (Table 4, Figure 3). We further found that the rela-

tionship between baseline plasma GFAP and CDR change was inverse when other scalable markers were included simultaneously (Table 4). This finding is likely related to the temporal dynamics of individual biomarkers along the disease continuum with recent evidence implying that plasma GFAP levels exhibited highest elevations in preclinical and early symptomatic stages of AD,[57] which may explain its negative associations in our total sample enriched for FTLD syndromes (Supplementary Table 9). Taken together, our results suggest that supplementing a plasma biomarker panel of pTau181, NfL, and GFAP with TabCAT-BHA is accurate in predicting longitudinal changes in disease severity across AD and FTLD syndromes, making this combination promising for disease monitoring.

Key strengths of this study include its focus on a novel combination of highly scalable, cost-effective, and accessible digital cognitive tools and plasma biomarkers, clinical heterogeneity of the study sample with regard to disease severity and neurodegenerative etiology, and greater representation of racially and ethnically diverse individuals compared to most prior studies.[8] At the same time, this study has a number of important limitations. First, not all participants in our sample completed Aβ-PET, and the prevalence of Aβ-PET positivity (55%) was higher compared to prior population-based estimates in older adults without dementia (22%).[58] Along with the fact that the Aβ-PET sample included only a few participants with SCI, these specifics of the study sample may limit generalizability of our findings to community settings. Our sample was also overrepresented for individuals with AD and FTLD, whereas other diseases such as Lewy body disease, which are relatively more common in general population, were not sufficiently represented. Second, we cannot exclude the possibility of our results being assay- and species-specific since we did not have access to other high performing assays (e.g., mass spectrometry-based Aβ[10]) or other pTau species (e.g., pTau217[15]). These limitations are important to consider given reported differences in performance between different Aβ assays[10,11] and plasma pTau species,[14,15] and more studies addressing the question of which combination of scalable plasma and clinical markers offers the best diagnostic and prognostic accuracy are needed. Also, the sample of this study was comprised of individuals with a low medical comorbidity burden, and given prior evidence suggesting differential performance of plasma biomarkers in individuals with certain comorbid conditions such as renal disease, stroke, or heart disease,[59] application of our findings to these clinical groups may be limited. Finally, while this study included a racially and ethnically diverse sample, replication of the results in more representative and socioeconomically diverse communities is needed to support the clinical validity of these markers across demographic groups.

In summary, our findings support complementary roles of scalable plasma and digital cognitive markers for detecting Aβ-PET positivity and predicting disease severity and longitudinal functional decline in diverse older adults with subjective and objective cognitive impairment. These low-cost, accessible technologies have the potential to complement or replace current diagnostic practices and can be used to inform future research on identification of optimal clinical implementation algorithms for early detection of ADRD.

CONFLICT OF INTEREST STATEMENT

None of the authors declare any competing financial interests relevant to the present study. J.C.R. is a site investigator for clinical trials sponsored by Eli Lilly and Eisai and receives funding from AlzOut and consulting fees from Roon Health, Inc. C.W. has received honoraria from the American Academy of Neurology and consulting fees from LCN Consulting. J.H.K. has received consulting fees from Biogen. BLM has received royalties from Cambridge University Press, Elsevier, Inc., Guilford Publications, Inc., Johns Hopkins Press, Oxford University Press, and Taylor & Francis Group; consulting fees from the Massachusetts General Hospital Alzheimer's Disease Research Center (ADRC) Scientific Advisory Board (SAB), Stanford University ADRC SAB, University of Washington ADRC SAB, Genworth SAB; and honoraria from the Global Summit on Neurodegenerative Diseases, Korean Dementia Society, Massachusetts General Hospital, National MS Society, Ochsner Neuroscience Institute, Providence Saint Joseph Medical Center, Taipei Medical University, University of California Irvine, University of California Los Angeles, and University of Texas. A.L.B. has served as a paid consultant to AGTC, Alector, Alzprotect, Amylyx, Arkuda, Arrowhead, Arvinas, Aviado, Boehringer Ingelheim, Denali, Eli Lilly, GSK, Humana, Life Edit, Merck, Modalis, Oligomerix, Oscotec, Roche, Transposon and Wave; has served as a site investigator for clinical trials sponsored by Biogen, Eisai, and Regeneron; and has received research support from the Rainwater Charitable Foundation, Bluefield Project to Cure FTD, GHR Foundation, Association for Frontotemporal Degeneration, Gates Ventures, Alzheimer's Drug Discovery Foundation, UCSF Parkinson's Spectrum Disorders Center and the University of California Cures AD Program. G.D.R. has received research funding from the Rainwater Charitable Foundation, Avid Radiopharmaceuticals, GE Healthcare, Genentech, Life Molecular Imaging; has served as a consultant for Alector, Eli Lilly, Genentech, GE Healthcare, Roche, Johnson & Johnson, and Merck; and is an Associate Editor for JAMA Neurology. K.L.P. has received research funding from Quest Diagnostics. ET, RLJ, LVV, CY, BC, ALL, AMR, CAG, SJE, BLT, SL, and PDA report no disclosures. Author disclosures are available in the supporting information.

CONSENT STATEMENT

The study was approved by the University of California San Francisco (UCSF) Committee on Human Research. All participants provided written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.