ARTICLE

OPEN ACCESS

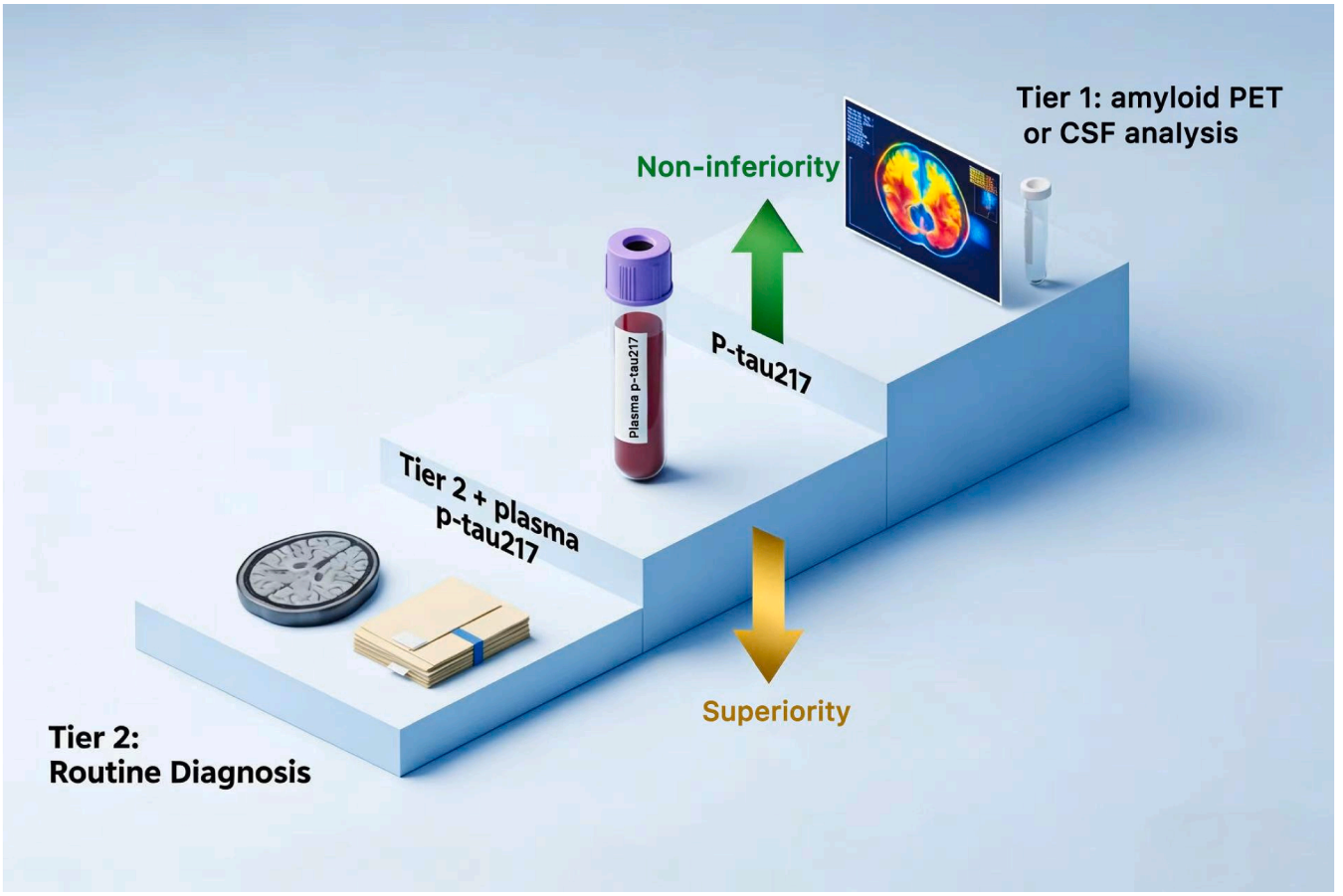
Plasma p-Tau217 improves diagnostic accuracy and clinician confidence in cognitive disorder classification

Yu-Yuan Huang,[1,6] Ling-Ling Li,[1,6] Rui-Xin Yao,[1,6] Jay Zengjun Dong,[2,6] Yi-Han Gan,[1] Yi-Lin Chen,[1] Ke-Liang Chen,[1] Shu-Fen Chen,[1] Ming-Yang Yuan,[1] Jia-Wei Xin,[3] Jun Wang,[4] Ya-Ru Zhang,[1] YuJing Wang,[2] Tzu-Chen Yen,[5] Mei Cui,[1,*] Yu Guo,[1,*] and Jin-Tai Yu[1,*]

*Correspondence: cuimei@fudan.edu.cn (M.C.); yucuoyihang@163.com (Y.G.); jintai_yu@fudan.edu.cn (J.-T.Y.)

Received: October 10, 2025; Accepted: January 16, 2026; https://doi.org/10.1016/j.xinn.2026.101272

GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Plasma p-tau217 testing revised the diagnosis in 30.2% of cases.
- Clinicians' diagnostic confidence rose by 14.3 percentage points after adopting the p-tau217 blood test.
- The integration of p-tau217 testing optimizes diagnostic workflows and healthcare resource use.

OPEN ACCESS

ARTICLE

The Innovation

Plasma p-Tau217 improves diagnostic accuracy and clinician confidence in cognitive disorder classification

Yu-Yuan Huang,[1,6] Ling-Ling Li,[1,6] Rui-Xin Yao,[1,6] Jay Zengjun Dong,[2,6] Yi-Han Gan,[1] Yi-Lin Chen,[1] Ke-Liang Chen,[1] Shu-Fen Chen,[1] Ming-Yang Yuan,[1] Jia-Wei Xin,[3] Jun Wang,[4] Ya-Ru Zhang,[1] YuJing Wang,[2] Tzu-Chen Yen,[5] Mei Cui,[1,*] Yu Guo,[1,*] and Jin-Tai Yu[1,*]

[1]Department of Neurology and National Center for Neurological Disorders, Huashan Hospital, State Key Laboratory of Brain Function and Disorders, MOE Frontiers Center for Brain Science, Shanghai Academy of Natural Sciences, New Cornerstone Science Laboratory, Shanghai Medical College, Fudan University, Shanghai 200040, China

[2]UltraDx Biotechnology (Shanghai) Co., Ltd., Shanghai 201203, China

[3]Department of Neurology, Fujian Medical University Union Hospital, Fujian Key Laboratory of Molecular Neurology and Institute of Neuroscience, Fujian Medical University, Fuzhou 350001, China

[4]Department of Neurology and Center for Clinical Neuroscience, Daping Hospital, Third Military Medical University, Chongqing 400038, China

[5]APRINOIA Therapeutics Co., Ltd., Suzhou 215000, China

[6]These authors contributed equally

*Correspondence: cuimei@fudan.edu.cn (M.C.); yucuoyihang@163.com (Y.G.); jintai_yu@fudan.edu.cn (J.-T.Y.)

Received: October 10, 2025; Accepted: January 16, 2026; https://doi.org/10.1016/j.xinn.2026.101272

Citation: Huang Y.-Y., Li L.-L., Yao R.-X., et al., (2026). Plasma p-Tau217 improves diagnostic accuracy and clinician confidence in cognitive disorder classification. The Innovation **7(6)**, 101272.

The clinical utility of plasma phosphorylated tau at threonine 217 (p-tau217) levels as a diagnostic tool for cognitive disorders in real-world settings remains uncertain. In this cross-sectional retrospective study, 738 consecutive subjects presenting with cognitive complaints at a memory clinic underwent diagnostic evaluation incorporating plasma p-tau217 alongside standard clinical assessments ("tier 2": routine neuroimaging and cognitive testing) and advanced biomarker testing ("tier 1": amyloid positron emission tomography [PET] imaging or cerebrospinal fluid [CSF] analysis). Diagnostic impact and confidence were assessed using clinician surveys. Incorporating plasma p-tau217 into the routine tier 2 diagnostic workup significantly influenced clinical decision-making, leading to diagnostic revisions in 30.2% of cases and improving overall diagnostic confidence from 65.1% to 79.4%. Plasma p-tau217 demonstrated high diagnostic accuracy for Alzheimer's disease (AD), with a sensitivity of 0.88 and a specificity of 0.84. Notably, its specificity was superior to tier 2 diagnoses, whereas its sensitivity did not differ significantly. Plasma p-tau217 also exhibited non-inferior performance to tier 1 approaches in the diagnostic distribution of AD, though with marginally lower diagnostic confidence. For non-AD diagnoses, plasma p-tau217 significantly impacted the classification of synucleinopathies and performed comparably to tier 1 methods. In conclusion, plasma p-tau217 meaningfully impacted diagnostic precision and confidence in subjects presenting to a real-world memory clinic, offering a minimally invasive, cost-effective, and accessible alternative to state-of-the-art examinations. As the global population ages and cognitive disorders become more prevalent, the integration of plasma p-tau217 into routine practice has the potential to streamline diagnostic workflows and enhance the efficient utilization of medical resources.

INTRODUCTION

The escalating prevalence of dementia and cognitive impairment within our aging society poses a significant public health concern.[1,2] Addressing this challenge requires an urgent refinement in routine diagnostic methodologies to facilitate targeted therapeutic interventions and optimize clinical care.[3] In real-world memory clinic practice, the initial diagnostic workup ("tier 2" diagnosis) of patients presenting with cognitive complaints typically comprises medical history, neuropsychological testing, standard laboratory blood tests, and brain magnetic resonance imaging (MRI). However, with the adoption of the amyloid/tau/neurodegeneration (ATN) framework for Alzheimer's disease (AD), core biomarker assessment via positron emission tomography (PET) and cerebrospinal fluid (CSF) analysis has become essential for precise biological classification, enabling a more accurate, state-of-the-art "tier 1" diagnosis.[4,5] Unfortunately, PET imaging—while highly informative—remains expensive and largely inaccessible outside specialized centers. Similarly, CSF analysis via lumbar puncture is constrained by its invasive nature, limited patient acceptability, and potential risk of complications.[6,7] These challenges underscore the need for a cost-effective, minimally invasive, and scalable diagnostic solution to better address the needs of patients presenting with cognitive complaints.[8,9]

Among the various plasma amyloid and tau markers, phosphorylated tau at threonine 217 (p-tau217) has emerged as a particularly promising candidate due to its strong association with cerebral amyloid pathology and its ability to distinguish AD from other conditions.[8,10–12] However, most prior studies evaluating the diagnostic performance of plasma p-tau217 have been conducted in controlled research settings or highly selected patient cohorts with strict inclusion and exclusion criteria. Consequently, the applicability of this peripheral biomarker for diagnosing patients with cognitive complaints in real-world memory clinic settings remains uncertain. We therefore designed the current study to assess the impact of plasma p-tau217 in unselected patients from routine clinical practice. Specifically, we evaluated its ability to prompt diagnostic revisions and enhance diagnostic confidence compared to conventional tier 2 diagnoses, which rely on standard clinical and laboratory data. Furthermore, we investigated whether incorporating plasma p-tau217 into tier 2 evaluations ("tier 2 + plasma p-tau217") could serve as a non-inferior alternative to the tier 1 state-of-the-art diagnostic standard, which typically involves more invasive and costly procedures—including PET imaging and/or CSF biomarker analysis. The study procedures are outlined in Figure 1.

MATERIALS AND METHODS

Study participants

This retrospective cohort study was conducted at the memory and neurology clinics of the National Center for Neurological Disorders, Huashan Hospital (Shanghai, China), between May 2019 and May 2024. Eligible patients were required to fulfill the following criteria: (1) report subjective cognitive decline (SCD), (2) have undergone amyloid PET imaging or CSF biomarker analysis to confirm or exclude AD pathology, and (3) complete a standardized diagnostic assessment, including clinical examination, neuropsychological evaluations, routine laboratory tests, and structural brain MRI. The study protocol adhered to the Declaration of Helsinki and received ethical approval from the institutional review board of Huashan Hospital (reference number: KY2024-1079). Written informed consent was obtained from all participants or their legal guardians following comprehensive disclosure of the study objectives and procedures.

Diagnostic procedure and diagnostic confidence

The assessment protocol is outlined in Figure 1. Based on neuropsychological assessments, participants were classified into the following cognitive stages: normal cognition (NC), mild cognitive impairment (MCI), or dementia.[13] The study neurologists first performed a routine tier 2 diagnosis (as detailed below). Two extended diagnostic conditions were then evaluated: one incorporating plasma p-tau217 (tier 2 + plasma p-tau217) and another incorporating biomarkers from CSF and/or PET (tier 1, as detailed below).

For each participant, clinicians determined (1) the underlying etiology and (2) the level of diagnostic confidence (Figure S1). All three diagnostic tiers for a given individual were assessed by the same evaluator to ensure consistency, with any discrepancies resolved by consulting a third senior specialist. The etiological framework initially divided cases into two primary categories: AD and non-AD. The AD group comprised three categories: AD dementia, MCI due to AD, and preclinical AD (cognitively unimpaired). Non-AD diagnoses encompassed a spectrum of disorders, including progressive supranuclear palsy (PSP),[14] corticobasal syndrome (CBS),[15] frontotemporal dementia (FTD),[16,17] synucleinopathies—including dementia with Lewy bodies (DLB),[18] Parkinson's disease dementia (PDD),[19,20]

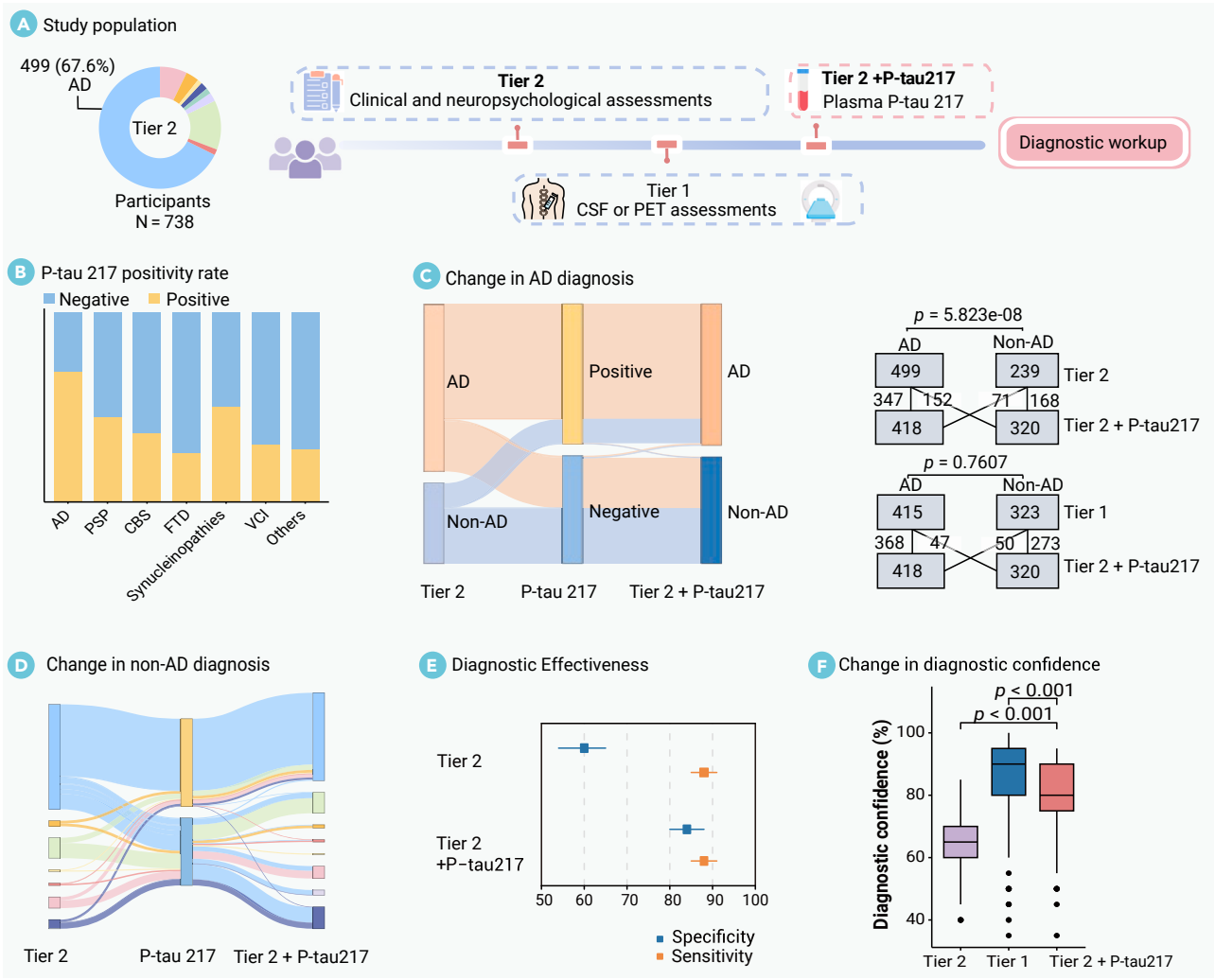


Figure 1. Clinical utility of plasma p-tau217 testing in a real-world tertiary memory clinic cohort (A) Schematic overview of the patient enrollment, diagnostic workflow, and integration of plasma p-tau217 testing within a real-world tertiary memory clinic setting. (B) Proportion of patients testing positive for plasma p-tau217 across the Tier 2 diagnostic groups. (C) Overall diagnostic reclassification after integrating plasma p-tau217 testing. (D) Reallocation of diagnoses between Alzheimer's disease (AD) and specific non-AD pathologies. (E) Receiver operating characteristic (ROC) curve demonstrating the accuracy of plasma p-tau217 against the reference standard. (F) Clinician-reported diagnostic confidence levels before and after disclosure of the plasma p-tau217 test result.

and multiple system atrophy (MSA)[21,22]—vascular cognitive impairment (VCI),[23] normal pressure hydrocephalus (NPH),[24,25] and mood and sleep disorders, among others. The "other conditions" category included spinocerebellar ataxia (SCA), autoimmune encephalitis,[26] epilepsy-associated dementia, and inherited metabolic disorders. Participants classified within the tier 1 or the tier 2 + plasma p-tau217 diagnostic frameworks who showed no cognitive deficits or AD biomarker evidence were classified as having SCD.[27] Diagnostic revisions were defined as transitions from an AD diagnosis to a non-AD diagnosis, or vice versa. Specifically, this meant reclassifying a non-AD case (e.g., FTD) to the AD continuum following a positive p-tau217 result, whereas reclassifying an AD case to FTD required an amyloid-negative profile plus supporting features such as frontotemporal atrophy on MRI. Diagnostic confidence at each tier was quantified using a visual analog scale ranging from 0% (not at all certain) to 100% (absolute certainty). A diagnostic confidence level of 90% was established as a high threshold that substantially exceeds the certainty of a clinical diagnosis alone (e.g., ~80% for probable AD without biomarkers) and approaches the certainty of a pathological confirmation.

Tier 2 routine diagnosis

Tier 2 diagnosis was based on routinely available information—including patient medical history, neuropsychological assessments, standard laboratory blood tests, and structural MRI findings. Medical history was obtained through detailed interviews with patients and their legal guardians. Cognitive function was evaluated using the mini-mental state examination (MMSE), the Beijing version of the Montreal cognitive assessment (MoCA-BJ), the auditory verbal learning test (AVLT), the Rey-Osterrieth complex figure (ROCF) test, the Boston naming test (BNT), the trail making test (TMT), the Stroop color and word test (SCWT), the clinical dementia rating (CDR) scale, the Hamilton anxiety scale (HAMA), the Hamilton depression scale (HAMD), and activities of daily living (ADL). Laboratory investigations included routine blood tests, serum levels of vitamin B12 and folic acid, thyroid function markers, and infection-related parameters such as HIV antibodies and the rapid plasma reagin test. Structural MRI was performed using a Discovery 750 3.0-T scanner (GE Healthcare, Milwaukee, WI, USA).

Tier 1 state-of-the-art diagnosis

Tier 1 diagnoses were established by integrating the routinely available data used for tier 2 evaluations with biomarker information obtained from PET imaging and/or CSF analysis, depending on the availability and clinical indication for each participant. To reflect the real-world context of this study, a tier 1 diagnosis was assigned to all patients for whom amyloid biomarker data were available. If a patient undergoes both PET and CSF examinations, the PET results will serve as the primary basis for the diagnostic process. Amyloid PET imaging was conducted using ^{18}F-florbetapir (AV45), while tau PET imaging utilized ^{18}F-florzolotau (formerly ^{18}F-APN-1607). Imaging results were classified as positive or negative based on cortical amyloid and tau deposition patterns. CSF samples for core biomarker analysis were obtained via lumbar puncture, centrifuged at 2,000*g* for 10 min within 1 h of collection, aliquoted into polypropylene tubes, and stored at −80°C until analysis. Levels of Aβ1-40, Aβ1-42, total tau (t-tau), and p-tau181 were measured in accordance with standardized protocols, as detailed in the supplemental methods.

Quantification of plasma p-tau217 levels and tier 2 + plasma p-tau217 diagnosis

Venous blood samples were obtained from all participants following an overnight fast using 5 mL EDTA-coated anticoagulant tubes (Vacutainer K2 EDTA tube; BD Diagnostics,

Table 1. General characteristics of the study participants

Characteristics	Entire sample	AD	Synucleinopathies	CBS	FTD	Mood and sleep disorders	NPH	PSP	VCI	Other conditions	*p*
No. of subjects	738	499	26	11	97	17	11	9	53	15	–
Age, years (median [IQR])	61.00 [56.00, 70.00]	59.00 [55.00, 69.00]	68.50 [63.25, 73.00]	62.00 [58.00, 66.50]	63.00 [55.00, 68.00]	58.00 [52.00, 69.00]	70.00 [63.50, 77.00]	66.00 [61.00, 70.00]	68.00 [63.00, 75.00]	63.00 [54.50, 68.00]	<0.001
Female	386 (52.3)	271 (54.3)	11 (42.3)	5 (45.5)	53 (54.6)	7 (41.2)	5 (45.5)	7 (77.8)	17 (32.1)	10 (66.7)	0.049
Male	352 (47.7)	228 (45.7)	15 (57.7)	6 (54.5)	44 (45.4)	10 (58.8)	6 (54.5)	2 (22.2)	36 (67.9)	5 (33.3)	0.049
Education, years (median [IQR])	9.00 [7.00, 12.00]	9.00 [6.00, 12.00]	9.00 [6.00, 11.50]	8.00 [5.00, 10.50]	9.00 [9.00, 12.00]	13.00 [9.75, 15.00]	12.00 [9.00, 12.00]	6.00 [5.00, 12.00]	9.00 [7.12, 12.00]	9.00 [5.00, 11.00]	0.052
MMSE (median [IQR])	17.00 [9.00, 23.75]	16.00 [9.00, 23.00]	12.00 [7.25, 17.50]	12.00 [11.00, 19.00]	17.00 [10.00, 22.00]	26.00 [25.00, 28.00]	21.00 [10.00, 24.00]	17.00 [8.00, 24.00]	21.00 [12.00, 24.00]	16.00 [11.50, 24.50]	<0.001
MoCA (median [IQR])	11.00 [5.00, 17.00]	10.00 [4.00, 17.00]	8.00 [6.00, 13.00]	9.00 [7.00, 9.00]	10.00 [5.50, 14.00]	23.00 [19.00, 24.00]	14.00 [7.00, 17.00]	10.00 [3.00, 13.00]	13.00 [8.00, 20.00]	8.00 [6.00, 18.00]	<0.001
Plasma p-tau217, pg/mL (median [IQR])	0.48 [0.23, 1.14]	0.77 [0.28, 1.36]	0.34 [0.20, 0.92]	0.31 [0.21, 0.42]	0.25 [0.19, 0.37]	0.21 [0.19, 0.28]	0.34 [0.31, 0.65]	0.26 [0.19, 0.43]	0.27 [0.23, 0.45]	0.25 [0.19, 0.37]	<0.001

Other conditions included spinocerebellar ataxia, autoimmune encephalitis, epilepsy-associated dementia, and inherited metabolic disorders. AD, Alzheimer's disease; FTD, frontotemporal dementia; VCI, vascular cognitive impairment; PSP, progressive supranuclear palsy; CBS, corticobasal syndrome; NPH, normal pressure hydrocephalus; MSA, multiple system atrophy; MMSE, mini-mental state examination; MoCA, Montreal cognitive assessment; IQR, interquartile range.

Sparks, MD, USA). Plasma was separated by centrifugation at 2,000*g* for 15 min within a 2 h window post-collection, aliquoted into 200 μL portions, and stored at −80°C until analysis. Plasma p-tau217 concentrations were quantified using the AlzPath Quanterix assay (Simoa pTau-217 Advantage V2 kit; Quanterix, MA, USA; lot numbers 999024 and 999048). All samples were analyzed in duplicate, processed in random order, and measured in batch testing at the end of sample collection. The interval between sample collection and plasma p-tau217 testing ranged from 2 to 62 months. Laboratory personnel were blinded to clinical and diagnostic data. The mean inter-batch coefficient of variation (CV) was <20%; to address this variability, four bridging samples and a linear regression adjustment were applied to align batch 1 measurements to batch 2 measurements. After calibration, the corrected p-tau217 values were considered reliable for analysis. Participants were classified as p-tau217 positive if their plasma levels exceeded the optimal cutoff value of 0.3514 pg/mL (supplemental methods). When performing the tier 2 + plasma p-tau217 diagnosis, neurologists were provided with both the quantitative plasma p-tau217 values and the corresponding dichotomized classification (positive or negative) based on the reference cutoff.

Model construction and threshold determination

Plasma p-tau217, age, and sex were assessed as potential predictors for constructing a logistic regression model of amyloid positivity (defined by CSF/PET), with model selection performed via bootstrapped backward elimination. The resulting model retained plasma p-tau217 as the key predictor and achieved an area under the curve (AUC) of 89% (95% confidence interval [CI]: 86.2%–91.7%). To further stratify participants, we applied three thresholding approaches that categorized individuals into low-, intermediate-, and high-risk groups of amyloid positivity according to predicted probabilities from the model. In this framework, lower probability thresholds were determined at the closest achievable sensitivities of 90% (to minimize the likelihood of missing Aβ-positive cases), whereas upper thresholds were defined at the closest achievable specificities of 90% (to reduce the risk of misclassifying Aβ-negative individuals as high risk).[28]

Statistical analysis

Data were summarized using descriptive statistics, including means and standard deviations (SDs), medians, interquartile ranges (IQRs), frequencies, and percentages. Continuous variables were analyzed using the Mann-Whitney U test or Kruskal-Wallis test, as appropriate. Categorical variables were assessed with chi-squared analysis, while McNemar's test was employed to evaluate diagnostic shifts. Receiver operating characteristic (ROC) curve analysis was applied to estimate the diagnostic accuracy of plasma p-tau217 under scrutiny. All calculations were performed using R, v.4.4.1 (R Foundation for Statistical Computing, Vienna, Austria), with all tests two-sided at a 5% level of significance.

RESULTS

Participant characteristics

The general characteristics of the 738 study participants (mean age: 61 years; 52.3% women) are presented in Table 1. Of these, 610 subjects underwent PET imaging, 144 received CSF testing, and 16 had both PET and CSF data available. Among those who completed PET imaging, all 610 received amyloid PET scans, with 369 (60.5%) testing positive. Tau PET scans were performed in 401 subjects, of whom 298 (74.3%) tested positive (Table S1). For participants with CSF biomarker data, 50 (34.7%) were classified as A+T+, 27 (18.8%) as A+T−, 20 (13.9%) as A−T+, and 47 (32.6%) as A−T− (Table S1).

Tier 2 diagnoses

Routine tier 2 diagnostic evaluations of the 738 participants identified 499 individuals (67.6%) with AD and 239 (32.4%) with non-AD etiologies. Among non-AD diagnoses, FTD was the most prevalent (13.1%, *n* = 97), followed by VCI (7.2%, *n* = 53), synucleinopathies (3.5%, *n* = 26), CBS (1.5%, *n* = 11), PSP (1.2%, *n* = 9), and other conditions (5.8%, *n* = 43) (Figure 2A). Diagnostic confidence for AD averaged 65.9% (SD: 9.7%) (Figure 3; Table S2). Within the non-AD group, CBS exhibited the highest diagnostic confidence (67.1%, SD: 9.0%), while PSP had the lowest (51.0%, SD: 2.2%).

Tier 1 diagnoses

Integration of core biomarker data—obtained through PET and/or CSF analysis—within routine tier 2 evaluations yielded revised tier 1 diagnoses: 415 participants (56.2%) with AD and 323 (43.8%) with non-AD etiologies. Non-AD diagnoses comprised FTD (15.2%, *n* = 112), VCI (7.9%, *n* = 58), SCD (3.1%, *n* = 23), synucleinopathies (2.2%, *n* = 16), CBS (1.8%, *n* = 13), PSP (1.4%, *n* = 10), and

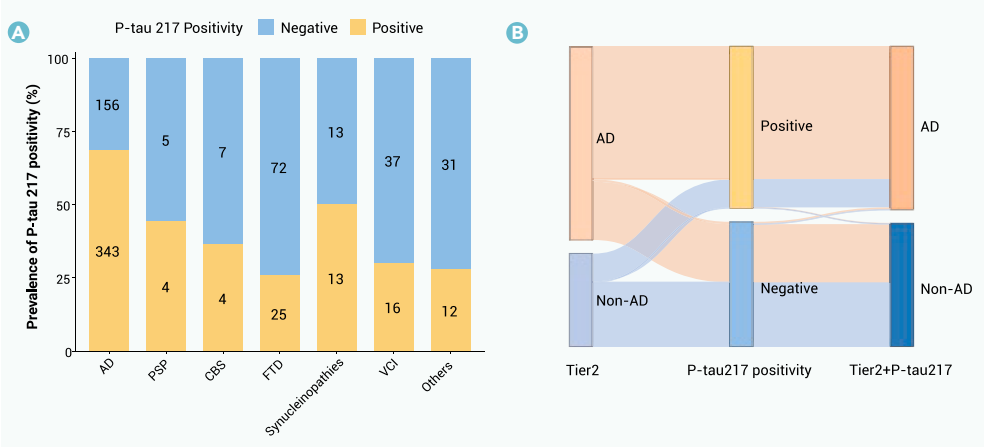


Figure 2. Distribution of plasma p-tau217 positivity according to tier 2 diagnoses and diagnostic revisions following incorporation of p-tau217 data (A) Distribution of plasma p-tau217 positivity according to clinical diagnoses. (B) Diagnostic revisions after incorporation of p-tau217 data in the entire study cohort. AD, Alzheimer's disease; PSP, progressive supranuclear palsy; CBS, corticobasal syndrome; FTD, frontotemporal dementia; VCI, vascular cognitive impairment.

other conditions (12.3%, *n* = 91). As a result, this biomarker-informed reclassification resulted in diagnostic revisions for 23.6% of cases (*n* = 174/738). Notably, 25.9% of participants initially diagnosed with AD under tier 2 (*n* = 129/499) were reclassified to non-AD etiologies, whereas 18.8% of non-AD cases (*n* = 45/239) shifted to AD (Figure 4C). Diagnostic confidence for AD under tier 1 increased to 90.2% (SD: 8.2%), reflecting greater certainty compared to tier 2 assessments (65.9%, $p < 0.001$). Among non-AD diagnoses, tier 1 confidence scores were highest for CBS (82.8%, SD: 9.4%), followed by VCI (81.5%, SD: 9.8%), others (80.7%, SD: 12.8%), FTD (80.2%, SD: 9.9%), synucleinopathies (79.9%, SD: 12.2%), and lowest for PSP (70.0%, SD: 9.4%) (Figure 3; Table S2).

Tier 2 + plasma p-tau217 diagnoses

Plasma p-tau217 positivity was detected in 417 participants (56.5%) across the cohort, with significantly higher rates observed in tier 2 AD diagnoses (68.7%, 343/499) compared to non-AD cases (31.0%, 74/239). The concentration of plasma p-tau217 varied significantly across diagnostic groups (Table S4; Figure S2). No significant difference was found when comparing the MCI-due-to-AD group to the preclinical-AD group. Among non-AD cases, p-tau217 positivity rates by etiology were as follows: synucleinopathies (50.0%), PSP (44.4%), CBS (36.4%), VCI (30.2%), FTD (25.8%), and other conditions (27.9%) (Figure 2A). We further evaluated the performance of p-tau217 in discriminating AD vs. non-AD diseases by generating ROC curves to assess its AUC values. Using a tier 1 diagnosis as the standard, the AUC of plasma p-tau217 for distinguishing AD from non-AD diseases in the overall sample was 89% (95% CI: 86%–91%). In cognitive subgroups (SCD, MCI, and dementia), the AUCs (95%, 88%, and 88%, respectively) did not differ significantly (Figure S3; Table S5). The discriminative accuracy of plasma p-tau217 for differentiating AD from specific non-AD disorders—including FTD, PSP, CBS, VCI, synucleinopathies, and other conditions—is presented in Figure S4 and Table S6.

Incorporation of plasma p-tau217 into the tier 2 diagnostic framework prompted diagnostic revisions in 30.2% of cases (*n* = 223/738; Figure 2B; Table S3). Notably, 20.6% of participants initially classified as AD under tier 2 (*n* = 152/738) were reclassified as non-AD diagnoses, whereas 9.6% (*n* = 71/738) shifted from non-AD to AD (Figure 4B). Diagnostic confidence for AD under the tier 2 + plasma p-tau217 framework averaged 83.2% (SD: 8.5%), reflecting improved certainty compared to tier 2 alone (65.9%) but remaining below tier 1 benchmarks (90.2%). Among non-AD etiologies, VCI demonstrated the highest clinician confidence (76.6%, SD: 8.0%), whereas PSP had the lowest (65.0%, SD: 5.0%) (Figure 3; Table S2).

Superiority of tier 2 + plasma p-tau217 vs. tier 2 diagnoses

Integration of plasma p-tau217 into the tier 2 framework significantly improved diagnostic specificity (84% vs. 60%, Δ24%, $p < 0.001$), though sensitivity remained unchanged (88% vs. 88%, Δ0%, $p = 1.000$) (Figure 5A). In the entire study cohort, the classification using the tier 2 strategy yielded a positive predictive value (PPV) of 74% and a negative predictive value (NPV) of 80%, whereas, when using the tier 2 + plasma p-tau217 strategy, the PPV increased to 88% and the NPV reached 85%. In subgroup analyses of participants with SCD, MCI, and dementia, the plasma p-tau217-enhanced framework (tier 2 + plasma p-tau217) significantly improved diagnostic specificity compared to tier 2 alone in participants with SCD (33% vs. 100%, Δ67%, $p < 0.001$) and MCI (51% vs. 87%, Δ36%, $p < 0.001$) but not in those with dementia (73% vs. 78%, Δ5%, $p = 0.432$) (Figures 5B–5D; Table S7).

The robustness of our findings was assessed using a dual-cutoff approach. This analysis revealed that the tier 2 + plasma p-tau217 framework (cutoffs: 0.236 and 0.455) provided significantly improved diagnostic specificity over tier 2 alone, with comparable sensitivity. For the group with p-tau217 levels outside the intermediate range (≥0.455 or <0.236), sensitivity was 89% (95% CI: 86%–92%) and specificity was 83% (95% CI: 76%–88%). The intermediate group (0.236–0.455) demonstrated a sensitivity of 79% (95% CI: 59%–92%) and a specificity of 87% (95% CI: 80%–92%).

To assess the clinical utility of plasma p-tau217 in refining diagnoses of non-AD neurodegenerative diseases, we compared tier 2 diagnoses with tier 2 + plasma p-tau217 classifications (Figure 6; Tables S8 and S9). Among 239 non-AD cases identified at tier 2, the tier 2 + plasma p-tau217 framework prompted significant diagnostic revisions (Table S10). The most pronounced reclassifications occurred in DLB, where 57.1% (12/21) of cases shifted to the AD continuum. Substantive revisions to AD also affected PSP (44.4%, 4/9) and CBS (27.3%, 3/11). FTD cases showed 25.8% (25/97) reclassification to AD, while VCI cases demonstrated 30.2% (16/53) revisions.

For non-AD tauopathies collectively (CBS, PSP, and FTD), diagnostic concordance between the tier 2 and the tier 2 + plasma p-tau217 frameworks was high ($p = 0.900$). Among the 499 participants with tier 2 AD diagnoses, the plasma p-tau217-enhanced framework prompted revisions in 30.5% of cases (*n* = 152/499). Specifically, reclassifications included FTD (18.4%, *n* = 28), SCD (15.1%, *n* = 23), VCI (14.5%, *n* = 22), synucleinopathies (2.0%, *n* = 3), CBS (2.0%, *n* = 3), and other conditions (48.0%, *n* = 73).

Non-inferiority of tier 2 + plasma p-tau217 vs. tier 1 diagnoses

We next investigated whether the tier 2 + plasma p-tau217 framework could serve as a non-inferior alternative to the state-of-the-art tier 1 reference standard. Among patients with an established tier 1 AD diagnosis, 88.7% were consistently classified as AD by the tier 2 + plasma p-tau217 framework (Figure 4A). Plasma p-tau217 testing, performed without PET/CSF data integration (Figure 4D), demonstrated diagnostic equivalence with tier 1 methods ($p = 0.761$), supporting its utility as a standalone biomarker. However, significant discordance was observed when benchmarking tier 2 + plasma p-tau217 diagnoses against the tier 1 reference standard ($p = 0.003$) in tauopathies, indicating divergent biomarker-driven classification patterns (Figures 6C; Table S9). Despite these strengths, the whole-sample diagnostic confidence for the tier 2 + plasma p-tau217 framework (79.4%, SD: 9.9%) was slightly reduced compared to that of tier 1 (86.0%, SD: 10.8%)—particularly in AD, VCI, FTD, and other etiologies (Table S2).

DISCUSSION

This cohort study provides the first comprehensive evaluation of plasma p-tau217's clinical utility across diverse cognitive disorders in an unselected tertiary memory clinic population, demonstrating how this emerging blood-based biomarker can be effectively integrated with established diagnostics in real-world scenarios. Accordingly, our findings demonstrate that incorporating plasma p-tau217 into routine clinical evaluations (tier 2) prompted diagnostic revisions in 30.2% of cases and increased overall diagnostic confidence from 65.1% to 79.4%. In addition, this biomarker exhibited enhanced

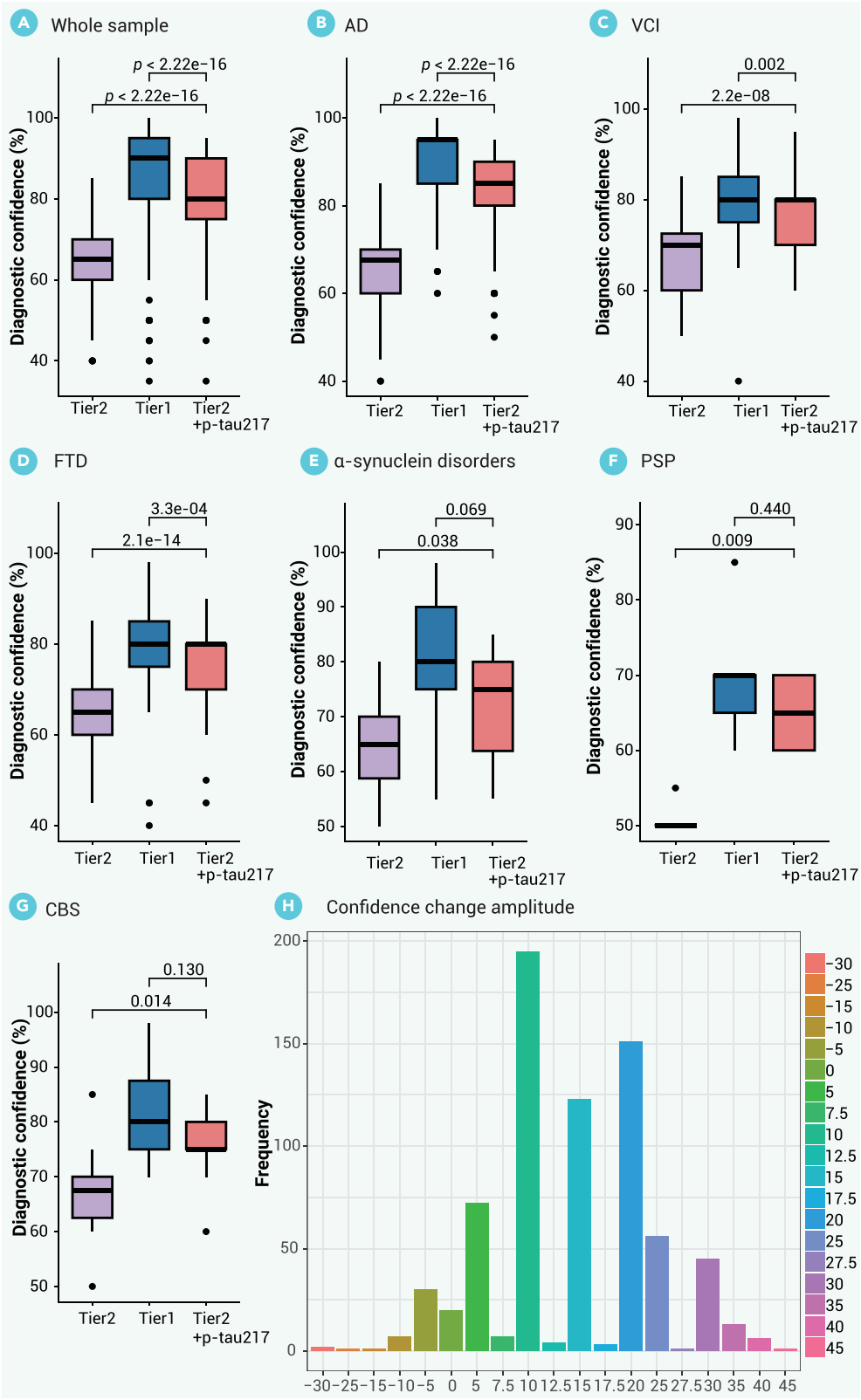


Figure 3. Diagnostic confidence of tier 2 + plasma p-tau217 diagnoses vs. tier 2 and tier 1 diagnoses

(A–G) Assessment of confidence levels in diagnoses made using the tier 2 + plasma p-tau217 framework vs. tier 2 and tier 1 diagnoses in the entire study cohort and stratified by disease categories. (H) Distribution of confidence differentials, calculated as the numerical difference between diagnostic confidence when using tier 2 + plasma p-tau217 vs. tier 2 diagnoses. AD, Alzheimer's disease; PSP, progressive supranuclear palsy; CBS, corticobasal syndrome; FTD, frontotemporal dementia; VCI, vascular cognitive impairment.

diagnostic specificity over tier 2 alone in specific patient subgroups, including SCD and MCI. Notably, the plasma p-tau217-enhanced framework (tier 2 + plasma p-tau217) was non-inferior to the state-of-the-art tier 1 reference standard (PET/CSF) for AD classification, albeit with marginally lower confidence.

In the current study, we intentionally refrained from restrictive inclusion and exclusion criteria to reflect a real-world clinical setting, which may explain the observed plasma p-tau217 positivity rate of approximately 50% during initial clinical diagnoses. Nonetheless, this finding is consistent with observations from primary care settings, where over half of patients with cognitive impairment remain undiagnosed or misdiagnosed due to limited access to state-of-the-art diagnostic tools.[29] Conversely, in cases verified within the AD continuum using PET imaging or CSF sampling, the positivity rate for plasma p-tau217 was significantly higher. Importantly, diagnostic revisions following plasma p-tau217 testing revealed a substantial proportion of participants transitioning from an initial diagnosis of AD to non-AD conditions, underscoring its ability to refine etiological diagnoses compared to standard tier 2 protocols. The divergent reclassification rates observed across cognitive disorders underscore both the high specificity of plasma p-tau217 for AD pathology and the inherent difficulties in clinically distinguishing FTD from AD. Moreover, only five participants retained an AD diagnosis despite negative plasma p-tau217 results, consistent with the biomarker's low false negative rate.[30] Taken together, these findings emphasize the critical role of integrating quantification of plasma p-tau217 levels into routine clinical practice, as both positive and negative results are pivotal for guiding accurate diagnostic decisions and tailoring subsequent treatment and management strategies. In this regard, failure to incorporate plasma p-tau217 quantification might potentially perpetuate diagnostic inaccuracies and inappropriate therapeutic interventions, ultimately compromising patient outcomes.

We believe that the robust performance of plasma p-tau217—which we found to be in line with state-of-the-art PET imaging or CSF examinations[31]—represents a potentially transformative advancement in AD diagnostics across both primary and specialized care settings.[32] Accordingly, the implementation of plasma p-tau217 testing holds the potential to diminish reliance on costly and invasive procedures while maintaining diagnostic precision[33,34]—an aspect particularly advantageous in resource-limited settings.[12,35] Furthermore, the stable accuracy of plasma p-tau217 facilitates a biologically anchored diagnosis of AD in real-world settings,[36] though its moderate sensitivity may reflect the clinical and pathological heterogeneity of our cohort. This contrasts with the superior discriminative ability reported in more homogeneous early-AD populations. While these findings support the clinical applicability of p-tau217, modest cross-center variations in performance and the complex early relationship between amyloid and tau pathology necessitate cautious individual interpretation. Consequently, further validation remains

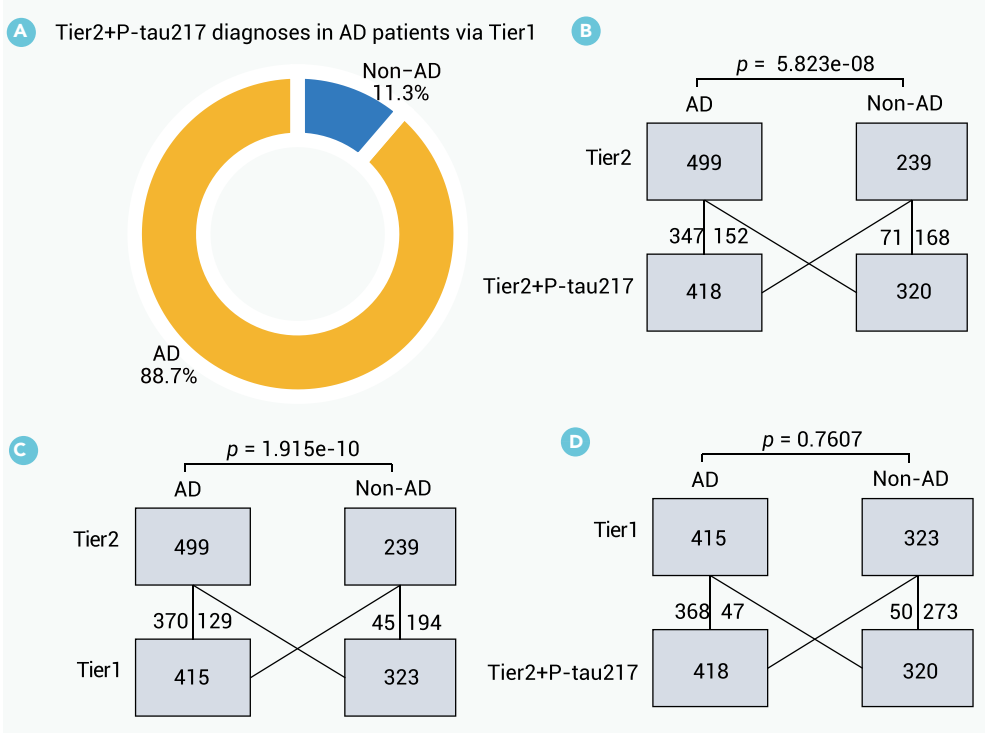


Figure 4. Comparative analysis of diagnostic reclassification prompted by plasma p-tau217 testing across different tiers (A) Pie chart of tier 2 + plasma p-tau217 diagnostic classifications specifically within the subpopulation of patients who received an Alzheimer's disease diagnosis through the state-of-the-art tier 1 assessment protocol. (B–D) Diagnostic comparisons between tier 2 diagnosis vs. tier 2 + plasma p-tau217 diagnosis, tier 2 diagnosis vs. tier 1 diagnosis, and tier 1 diagnosis vs. tier 2 + plasma p-tau217 diagnosis. Numbers outside the boxes indicate the number of individuals reclassified when moving from one diagnostic step to the next.

necessary to establish standardized cutoffs and evaluate longitudinal performance in diverse populations.[37,38]

Early biomarker-based etiological characterization of cognitive disorders, particularly in SCD, is critical for potentially modifying disease progression, which typically evolves over decades.[4,39] A significant finding from our investigation is that plasma p-tau217 incorporation into the diagnostic workflow demonstrated high specificity relative to a tier 2 diagnosis across the SCD-MCI spectrum, consistent with evidence that plasma p-tau217 may detect incipient cerebral amyloid pathology.[33,40,41] Conversely, this observation confirms plasma p-tau217's capacity to reliably exclude non-AD pathology in early disease stages, minimizing misdiagnosis risk. Such diagnostic precision can have substantial implications for optimizing clinical management and achieving cost-effectiveness in clinical practice.

Here, we have shown that plasma p-tau217 may serve as an effective biomarker for identifying AD pathology in non-AD cognitive disorders, facilitating diagnostic reclassifications in line with the tier 1 framework. These observations are also in accordance with data obtained from neuropathology cohorts,[12] emphasizing the specificity of p-tau217 for AD-related tau pathology. While the relatively limited sample sizes for PSP and CBS in our investigation should prompt disease-specific validation studies,[42] the substantial improvement in diagnostic confidence following plasma p-tau217 assessment underscores its potential to optimize clinical decision-making in routine practice. In addition, this investigation represents the first demonstration that plasma p-tau217 contributes significantly to the diagnosis of synucleinopathies with performance comparable to tier 1 state-of-the-art modalities.

The principal strength of this investigation derives from its implementation in a real-world clinical setting, incorporating consecutive subjects across a large spectrum of cognitive disorders. Additionally, uniform plasma processing and analytical methods throughout the study ensured standardization and technical homogeneity. However, our findings should be interpreted within the context of certain limitations. First, the study population consisted exclusively of Han Chinese individuals from a single memory clinic—which may constrain generalizability and external validity. Second, the absence of neuropathological confirmation through autopsy verification represents an important caveat in definitively establishing plasma p-tau217 diagnostic accuracy. Third, our study focused on identifying the predominant pathology responsible for the clinical syndrome, a pragmatic approach given the current therapeutic landscape. However, we acknowledge that this does not capture the full spectrum of co-pathologies, which are common and may influence clinical presentation and disease progression. The investigation of mixed pathologies and their interactions represents a critical and necessary direction for future research. Finally, our cohort's

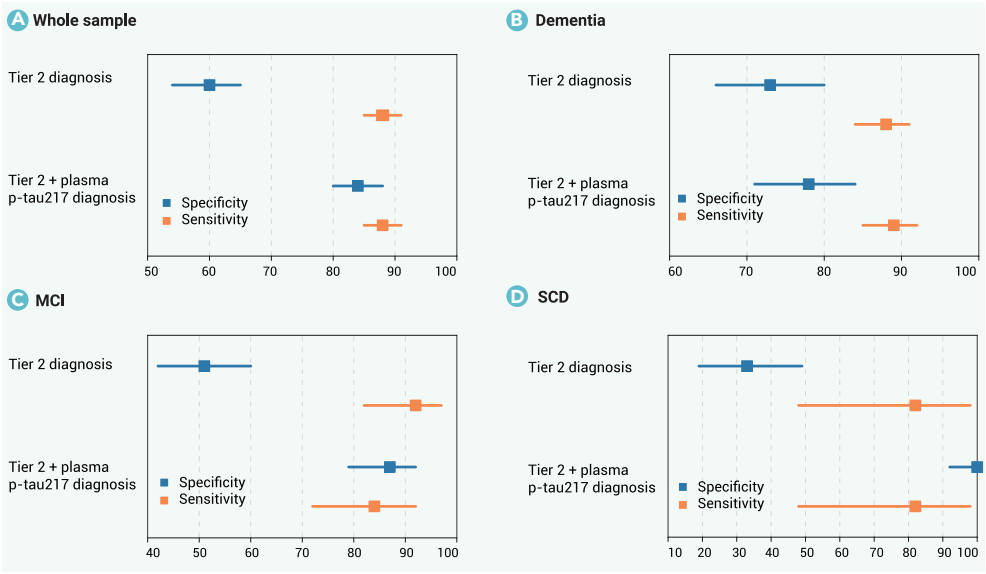


Figure 5. Sensitivities and specificities of AD diagnoses obtained via plasma p-tau217 quantification Here, CSF/PET-defined amyloid-β (Aβ) positivity was applied as the gold standard for AD diagnosis. In this context, the sensitivity and specificity of tier 2 diagnosis and tier 2 + plasma p-tau217 diagnosis were evaluated. Performance metrics in the entire study cohort (A), dementia subgroup (B), mild cognitive impairment subgroup (C), and subjective cognitive decline subgroup (D) are shown. In all four images, blue squares represent specificity, and orange squares represent sensitivity, with horizontal lines showing 95% confidence intervals. The *x* axis displays percentages.

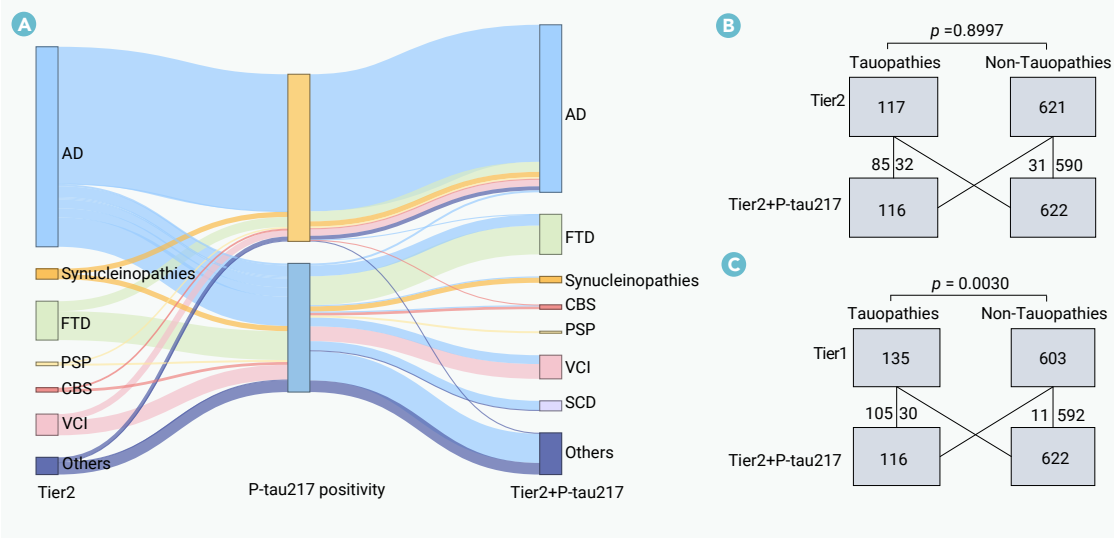


Figure 6. Diagnostic reclassification prompted by plasma p-tau217 testing across non-AD cognitive disorders (A) Sankey diagram illustrating the reclassification of diagnoses across different non-AD neurodegenerative disorders following plasma p-tau217 testing, as stratified by the p-tau217 status (negative/positive). (B and C) Diagnostic reclassification between tauopathies vs. non-tauopathies: tier 2 vs. tier 2 + plasma p-tau217 diagnosis (B) and tier 1 vs. tier 2 + plasma p-tau217 diagnosis (C). Numbers outside the boxes indicate the number of individuals reclassified when moving from one diagnostic step to the next.

dependence on the availability of PET or CSF data, determined by real-world clinical practice rather than a strict protocol, introduces a potential selection bias. While this limits the generalizability of our findings to all patient populations, it simultaneously reflects the pragmatic diagnostic challenges and heterogeneity inherent in actual clinical settings.

In conclusion, plasma p-tau217 assessment, when integrated with routine diagnostic workups, holds promise for early and optimized identification of AD in real-world memory clinics. Notably, this minimally invasive blood-based biomarker was found to facilitate diagnostic reclassification and improve clinician confidence, potentially reducing reliance on more resource-intensive diagnostic modalities.

RESOURCE AVAILABILITY

Materials availability

This research did not generate new unique materials.

Data and code availability

The data used and analyzed in this study are available from the corresponding author upon reasonable request. The codes that support the findings of the present study are available from the corresponding authors upon request. All models were built using publicly available packages and functions in the R programming language.

FUNDING AND ACKNOWLEDGMENTS

This study was supported by the Ministry of Science and Technology of China (STI2030-Major Projects 2030 2021ZD0201806, and 2022ZD0211600). J.T.-Y, as a SANS Scholar, was supported by grants from the Brain Science and Brain-like Intelligence Technology-National Science and Technology Major Project (2022ZD0211600); Shanghai Medicine and Health Development Foundation; the National Natural Science Foundation of China (82530047, 82588301, and 82271471); the Leading Project of the Discipline Breakthrough Plan of the Ministry of Education (JYB2025XDXM604); the Excellent Academic Research Leader Program of Shanghai (23XD1420400); the Changping Laboratory (2025B-07-35); the Lin Gang Laboratory (LGL-3241-PDA030200); the Shanghai Academy of Natural Sciences; the New Cornerstone Science Foundation; the Zhangjiang Lab; the Tianqiao and Chrissy Chen Institute; and the State Key Laboratory of Brain Function and Disorders of Ministry of Education, Fudan University. Y.Y.-H. was funded by the Research Fund of the Shanghai Municipal Health Commission (20234Y0307), the National Natural Science Foundation of China (82401647), and the Fudan University Young Clinical Investigator Development Program (DGF828024-3/018). Y.G. was funded by the National Natural Science Foundation of China (82501695), the National Postdoctoral Program for Innovative Talents (BX20240073), and the China Postdoctoral Science Foundation (2024M760562). Y.R.-Z. was funded by the Shanghai Municipal Health Commission Health Industry Clinical Research Special Project (20244Y0124). Further, we would like to express our thanks for the support of the Zhangjiang Lab; the Tianqiao and Chrissy Chen Institute; and the State Key Laboratory of Neurobiology and Frontiers Center for Brain Science of the Ministry of Education, Fudan University. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. We sincerely thank all study participants for their contributions. We also express our gratitude to Prof. Enzo Emanuele for his valuable assistance.

AUTHOR CONTRIBUTIONS

Conceptualization, J.-T.Y., Y.G., and M.C.; study design, J.-T.Y., Y.G., and M.C.; data interpretation, J.-T.Y., Y.G., M.C., Y.-Y.H., L.-L.L., R.-X.Y., J.Z.D., Y.-H.G., and Y.-L.C.; writing original draft, Y.-Y.H., L.-L.L., R.-X.Y., J.Z.D., Y.-H.G., and Y.-L.C.; writing – review & editing, all authors; data collection, Y.-Y.H., L.-L.L., R.-X.Y., J.Z.D., Y.-H.G., and Y.-L.C.; data analysis, Y.-Y.H., L.-L.L., R.-X.Y., J.Z.D., Y.-H.G., and Y.-L.C.

DECLARATION OF INTERESTS

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.xinn.2026.101272.

REFERENCES

1. Chen, S. and Kuper, H. (2023). Tracing the temporal trends of modifiable risk factors in dementia: insights from the English Longitudinal Study of Ageing (2004-2019). *Lancet* **402**:S34. DOI:10.1016/S0140-6736(23)02078-0
2. Jessen, F., Amariglio, R.E., Buckley, R.F. et al. (2020). The characterisation of subjective cognitive decline. *Lancet Neurol.* **19**:271–278. DOI:10.1016/S1474-4422(19)30368-0
3. Abbott, A. (2023). Conquering Alzheimer's: a look at the therapies of the future. *Nature* **616**:26–28. DOI:10.1038/d41586-023-00954-w
4. Scheltens, P., De Strooper, B., Kivipelto, M. et al. (2021). Alzheimer's disease. *Lancet* **397**:1577–1590. DOI:10.1016/S0140-6736(20)32205-4
5. Ritchie, K. and Lovestone, S. (2002). The dementias. *Lancet* **360**:1759–1766. DOI:10.1016/S0140-6736(02)11667-9
6. Guo, Y., You, J., Zhang, Y. et al. (2024). Plasma proteomic profiles predict future dementia in healthy adults. *Nat. Aging* **4**:247–260. DOI:10.1038/s43587-023-00565-0
7. Teunissen, C.E., Verberk, I.M.W., Thijssen, E.H. et al. (2022). Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. *Lancet Neurol.* **21**:66–77. DOI:10.1016/S1474-4422(21)00361-6
8. Barthelemy, N.R., Salvado, G., Schindler, S.E. et al. (2024). Highly accurate blood test for Alzheimer's disease is similar or superior to clinical cerebrospinal fluid tests. *Nat Med* **30**:1085–1095. DOI:10.1038/s41591-024-02869-z
9. Hansson, O., Blennow, K., Zetterberg, H. et al. (2023). Blood biomarkers for Alzheimer's disease in clinical practice and trials. *Nat. Aging* **3**:506–519. DOI:10.1038/s43587-023-00403-3

10. Mohs, R.C., Beauregard, D., Dwyer, J. et al. (2024). The Bio-Hermes Study: Biomarker database developed to investigate blood-based and digital biomarkers in community-based, diverse populations clinically screened for Alzheimer's disease. *Alzheimer's Dement.* **20**:2752–2765. DOI:10.1002/alz.13722
11. Ashton, N.J., Puig-Pijoan, A., Milà-Alomà, M. et al. (2023). Plasma and CSF biomarkers in a memory clinic: Head-to-head comparison of phosphorylated tau immunoassays. *Alzheimer's Dement.* **19**:1913–1924. DOI:10.1002/alz.12841
12. Palmqvist, S., Janelidze, S., Quiroz, Y.T. et al. (2020). Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. *JAMA* **324**:772–781. DOI:10.1001/jama.2020.12134
13. American Psychiatric Association D.-T. F. (2013). Diagnostic and Statistical Manual of Mental Disorders: DSM-5™, 5th ed. (American Psychiatric Publishing, Inc.). DOI:10.1176/appi.books.9780890425596
14. Höglinger, G.U., Respondek, G., Stamelou, M. et al. (2017). Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. *Mov. Disord.* **32**:853–864. DOI:10.1002/mds.26987
15. Armstrong, M.J., Litvan, I., Lang, A.E. et al. (2013). Criteria for the diagnosis of corticobasal degeneration. *Neurology* **80**:496–503. DOI:10.1212/WNL.0b013e31827f0fd1
16. Gorno-Tempini, M.L., Hillis, A.E., Weintraub, S. et al. (2011). Classification of primary progressive aphasia and its variants. *Neurology* **76**:1006–1014. DOI:10.1212/WNL.0b013e31821103e6
17. Rascovsky, K., Hodges, J.R., Knopman, D. et al. (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* **134**:2456–2477. DOI:10.1093/brain/awr179
18. McKeith, I.G., Boeve, B.F., Dickson, D.W. et al. (2017). Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology* **89**:88–100. DOI:10.1212/wnl.0000000000004058
19. Litvan, I., Goldman, J.G., Tröster, A.I. et al. (2012). Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov. Disord.* **27**:349–356. DOI:10.1002/mds.24893
20. Postuma, R.B., Berg, D., Stern, M. et al. (2015). MDS clinical diagnostic criteria for Parkinson's disease. *Mov. Disord.* **30**:1591–1601. DOI:10.1002/mds.26424
21. Gilman, S., Wenning, G.K., Low, P.A. et al. (2008). Second consensus statement on the diagnosis of multiple system atrophy. *Neurology* **71**:670–676. DOI:10.1212/01.wnl.0000324625.00404.15
22. Wenning, G.K., Stankovic, I., Vignatelli, L. et al. (2022). The Movement Disorder Society Criteria for the Diagnosis of Multiple System Atrophy. *Mov. Disord.* **37**:1131–1148. DOI:10.1002/mds.29005
23. Sachdev, P., Kalaria, R., O'Brien, J. et al. (2014). Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. *Alzheimer Dis. Assoc. Disord.* **28**:206–218. DOI:10.1097/wad.0000000000000034
24. Relkin, N., Marmarou, A., Klinge, P. et al. (2005). Diagnosing idiopathic normal-pressure hydrocephalus. *Neurosurgery* **57**:S4–S16. DOI:10.1227/01.neu.0000168185.29659.c5
25. Nakajima, M., Yamada, S., Miyajima, M. et al. (2021). Guidelines for Management of Idiopathic Normal Pressure Hydrocephalus (Third Edition): Endorsed by the Japanese Society of Normal Pressure Hydrocephalus. *Neurol. Med.-Chir.* **61**:63–97. DOI:10.2176/nmc.st.2020-0292
26. Graus, F., Titulaer, M.J., Balu, R. et al. (2016). A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol.* **15**:391–404. DOI:10.1016/s1474-4422(15)00401-9
27. Jessen, F., Amariglio, R.E., van Boxtel, M. et al. (2014). A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimer's Dement.* **10**:844–852. DOI:10.1016/j.jalz.2014.01.001
28. Brum, W.S., Cullen, N.C., Janelidze, S. et al. (2023). A two-step workflow based on plasma p-tau217 to screen for amyloid β positivity with further confirmatory testing only in uncertain cases. *Nat. Aging* **3**:1079–1090. DOI:10.1038/s43587-023-00471-5
29. Hansson, O. (2021). Biomarkers for neurodegenerative diseases. *Nat. Med.* **27**:954–963. DOI:10.1038/s41591-021-01382-x
30. Thijssen, E.H., La Joie, R., Strom, A. et al. (2021). Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study. *Lancet Neurol.* **20**:739–752. DOI:10.1016/S1474-4422(21)00214-3
31. Jack, C.R., Jr., Andrews, J.S., Beach, T.G. et al. (2024). Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimer's Dement.* **20**:5143–5169. DOI:10.1002/alz.13859
32. Palmqvist, S., Tideman, P., Mattsson-Carlgren, N. et al. (2024). Blood Biomarkers to Detect Alzheimer Disease in Primary Care and Secondary Care. *JAMA* **332**:1245–1257. DOI:10.1001/jama.2024.13855
33. Ashton, N.J., Brum, W.S., Di Molfetta, G. et al. (2024). Diagnostic Accuracy of a Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer Disease Pathology. *JAMA Neurol.* **81**:255–263. DOI:10.1001/jamaneurol.2023.5319
34. Devanarayan, V., Doherty, T., Charil, A. et al. (2024). Plasma pTau217 predicts continuous brain amyloid levels in preclinical and early Alzheimer's disease. *Alzheimer's Dement.* **20**:5617–5628. DOI:10.1002/alz.14073
35. Giacomucci, G., Crucitti, C., Ingannato, A. et al. (2025). The two cut-offs approach for plasma p-tau217 in detecting Alzheimer's disease in subjective cognitive decline and mild cognitive impairment. *Alzheimer's Dement.* **17**:e70116. DOI:10.1002/dad2.70116
36. Gonzalez-Ortiz, F., Ferreira, P.C.L., González-Escalante, A. et al. (2024). A novel ultrasensitive assay for plasma p-tau217: Performance in individuals with subjective cognitive decline and early Alzheimer's disease. *Alzheimer's Dement.* **20**:1239–1249. DOI:10.1002/alz.13525
37. van Dyck, C.H., Swanson, C.J., Aisen, P. et al. (2023). Lecanemab in Early Alzheimer's Disease. *N. Engl. J. Med.* **388**:9–21. DOI:10.1056/NEJMoa2212948
38. Sims, J.R., Zimmer, J.A., Evans, C.D. et al. (2023). Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA* **330**:512–527. DOI:10.1001/jama.2023.13239
39. Swaddiwudhipong, N., Whiteside, D.J., Hezemans, F.H. et al. (2023). Pre-diagnostic cognitive and functional impairment in multiple sporadic neurodegenerative diseases. *Alzheimer's Dement.* **19**:1752–1763. DOI:10.1002/alz.12802
40. Mila-Aloma, M., Ashton, N.J., Shekari, M. et al. (2022). Plasma p-tau231 and p-tau217 as state markers of amyloid-beta pathology in preclinical Alzheimer's disease. *Nat Med* **28**:1797–1801. DOI:10.1038/s41591-022-01925-w
41. Ferreira, P.C.L., Therriault, J., Tissot, C. et al. (2023). Plasma p-tau231 and p-tau217 inform on tau tangles aggregation in cognitively impaired individuals. *Alzheimer's Dement.* **19**:4463–4474. DOI:10.1002/alz.13393
42. VandeVrede, L., La Joie, R., Thijssen, E.H. et al. (2023). Evaluation of Plasma Phosphorylated Tau217 for Differentiation Between Alzheimer Disease and Frontotemporal Lobar Degeneration Subtypes Among Patients With Corticobasal Syndrome. *JAMA Neurol.* **80**:495–505. DOI:10.1001/jamaneurol.2023.0488