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Critical Reviews in Clinical Laboratory Sciences

ISSN: 1040-8363 (Print) 1549-781X (Online) Journal homepage: www.tandfonline.com/journals/ilab20

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To cite this article: Hans Frykman (2026) Analytical considerations and clinical utility of plasma phosphorylated Tau217, Critical Reviews in Clinical Laboratory Sciences, 63:2, 124-134, DOI: 10.1080/10408363.2025.2551648

To link to this article: https://doi.org/10.1080/10408363.2025.2551648

Published online: 15 Sep 2025.

CRITICAL REVIEWS IN CLINICAL LABORATORY SCIENCES
2026, VOL. 63, NO. 2, 124–134
https://doi.org/10.1080/10408363.2025.2551648

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INVITED REVIEW

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Analytical considerations and clinical utility of plasma phosphorylated Tau217

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ABSTRACT

Blood-based biomarkers are an easily available and practical tool for Alzheimer's disease (AD) screening and diagnosis. Plasma phosphorylated Tau217 (p-tau217) is the front-runner candidate for AD diagnosis due to its strong correlation with core AD pathology determined either by cerebrospinal fluid biomarker (CSF) and positron emission tomography (PET) or postmortem examination. While plasma p-tau217 is firmly associated with AD pathology, it is crucial to evaluate its performance in distinguishing AD from mixed pathologies, as brain autopsies have shown the coexisting of AD pathology with other related types of dementia. Moreover, the measurement of AD biomarkers will be a crucial element in defining eligibility for disease-modifying treatment in clinical practice. Moreover, plasma p-tau217 is a highly efficacious biomarker in the early detection of Aβ pathology, making it a feasible test for AD screening in clinical practice. Several assays, including the ALZpath p-tau217 assay and the Fujirebio plasma p-tau217 assay, have been made commercially available for research use. A few studies analytically and clinically have validated these immunoassays as laboratory diagnostic tests for AD diagnosis and differentiating from non-AD neurodegenerative disorders in clinical practice.

ARTICLE HISTORY
Received 17 May 2025
Revised 17 August 2025
Accepted 20 August 2025

KEYWORDS
Alzheimer's disease; biological diagnosis B; blood based biomarkers; p-tau217; analytical validation

Background

Alzheimer's Disease (AD) constitutes about two-thirds of dementia cases and currently more than 55 million people worldwide live with dementia and AD may contribute to 60 – 70% of them. It is estimated that its prevalence will be tripled by 2050 and 43% of these patients will need high levels of care [1,2]. The foremost neurodegenerative diseases are defined by misfolding the normal proteins (proteinopathy) and accumulation of them in the central nervous system, which supports the potential for mechanism-based proteomic biomarkers to be detected in biofluids [3,4]. AD is a double proteinopathy with its fundamental neuropathologic features defined by amyloid-beta (Aβ) plaques and neurofibrillary tangles with cumulative hyperphosphorylated tau (ptau) [5,6] Aβ is a small peptide derived by secretase cleavage of the amyloid precursor protein (APP) [5,6]. The deposition of Aβ in the brain as an extracellular neuritic ß-amyloid plaques and in the cerebral vasculature leads to neurotoxicity, dementia, and cerebral amyloid angiopathy. Tau is a phosphoprotein and a microtubule-associated protein (MAP); its essential role is the stabilization of axonal microtubules [5,6]. Aggregation of abnormal ptau in the neuronal cytoplasm occurs in AD and other tauopathies such as progressive supranuclear palsy (PSP) and Parkinson's disease (PD). The presence of ptau deposits in various morphologies, many years before the onset of clinical findings, is the common neuropathological feature of these conditions [7,8]. Therefore, the role of biomarkers in the early diagnosis of AD is imperative and pathophysiologic and topographical biomarkers have helped clinicians to recognize and distinguish AD phenotypes from other types of dementia and neurodegenerative diseases. Pathophysiologic biomarkers, such as amyloid and tau PET, CSF and plasma, amyloid β, tau proteins, and NfL concentrations play a crucial role in this diagnostic improvement. Topographic biomarkers, such as fluorodeoxyglucose (FDG)-PET, and MRI, assess the focal distribution of AD pathologies [9].

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The CSF Aβ42/Aβ40 ratio measurement is a sturdy biomarker in detecting Aβ pathology and AD diagnosis [10]. A prominent feature of the Aβ42/Aβ40 ratio is that it can be abnormal many years before symptomatic stages [10–13]. While this feat makes it a really early marker for AD pathology, it is important to remark that not all individuals with abnormalities in the AB ratio will progress to symptomatic stages. Hence the need of complementing AB measurements with biomarkers that strongly associate with clinical progression [10].

Several specific assays for measuring AD blood biomarkers including p-tau217 have been developed during last years. All ptau available tests measure phosphorylated forms of tau using specific antibodies that target the N-terminal or mid-domain of the protein other than its full-length or C-terminus [14–16]. Plasma p-tau217 can distinguish AD from other forms of neurodegenerative dementia and tauopathies with similar diagnostic performance to the FDA-approved CSF biomarkers and tau-PET imaging. Moreover, a number of studies have demonstrated that plasma p-tau217 is an accurate marker to predict AD progression in patients with either minimal cognitive impairment (MCI) or subjective cognitive decline (SCD), and it is better for AD diagnosis in its earlier stages [17–19].

In this review we discus the biological configuration and normal function of tau protein, tau phosphorylation at different threonine sites, biochemistry of tau isoforms in normal brain and biofluids and their detection feasibility in plasma using novel technologies. Then we critically review the analytical and clinical validations of plasma p-tau217 comparing to p-tau181 and p-au231 and other established biomarkers.

Normal and abnormal configuration of tau

Tau stands for tubulin associated unit, a multifaceted microtubule-associated protein (MAP), predominantly presents in neurons. It plays an important role in stabilizing microtubules and contributing to neuronal function and plasticity [20,21]. In the mature neurons, a tau protein consists of six isoforms with 352 to 441 amino acids and is encoded by the microtubule-associated protein tau (MAPT) gene on chromosome 17q21 [22–24]. It includes four regions: an amino-terminal, a mid-region, a microtubule-binding region, and a carboxy terminus (Figure 1). The differences between its isoforms are based on the presence of either three (3 R) or four (4 R) microtubule-binding repeats (R) of 31–32 amino acids, and in the inclusion of one (1 N), two (2 N), or no (0 N) amino-terminal insertions of 29 amino acids. Consequently, resulting from different splicing patterns

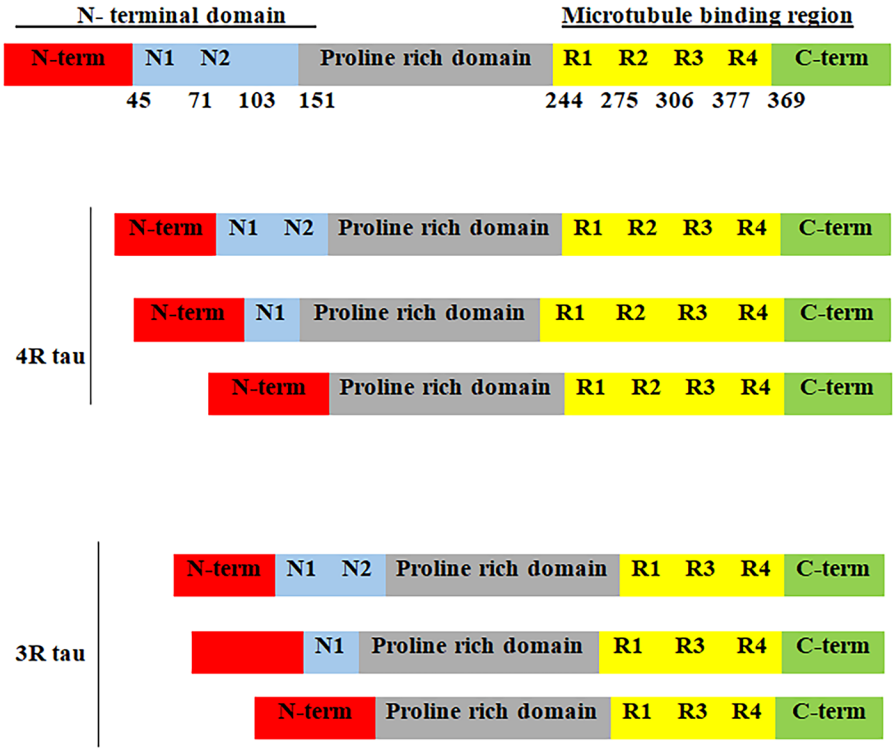

Figure 1. Tau protein structure that includes a predominantly acidic N-terminal region, a proline-rich Central region, and a relatively neutral C-terminal region. The tau isoforms vary in containing either three (3 R) or four (4 R) microtubule-binding repeats (R) as well as one (1 N), two (2 N), or zero (0 N) amino-terminal insertions.

of tau pre-mRNA there are three 3R tau isoforms (0N3R, 1N3R, 2N3R) and three 4R tau isoforms (0N4R, 1N4R, 2N4R). The 2N4R is the largest isoform with 441 amino acids, and the 0N3R isoform is the smallest with 352 amino acids [22,24–26].

These normal taus are natively unfolded, and their tendency toward misfolding and accumulation in intracellular and extracellular situations is minimal. Despite phosphorylation being a key factor in the physiological modification of tau, excessive phosphorylation can lead to the self-aggregation of p-tau, a hallmark of tauopathies [27–31]. Although several posttranslational modifications, including truncation, acetylation, ubiquitination, and sumoylation, can lead to tau aggregation, abnormal tau phosphorylation in AD has been broadly studied. Approximate 85 possible phosphorylation sites are in the longest tau isoform, of which 45 have been observed experimentally to be phosphorylated [32–34].

Biological diagnosis of AD

The clinical features of AD are related to its pathological processes. AD neuropathological cascades start years before its apparent clinical presentation and spread in a consistent pattern with subsequent neuroanatomical and neurophysiological changes. Therefore, clinical findings of AD are heterogenous but in a continuum from cognitively unimpaired through mild cognitive impairment (MCI), to severe dementia. The picture is even rendered more heterogeneous with the inclusion of atypical AD. MCI can be a prodromal phase of AD and patients with amnestic MCI progress to AD at an approximate rate of 10–15% per year whilst 11%–33% of them developing it within the first 2 years. However, 50% of patients with MCI will return to normal in the follow up evaluations. Thus, the accurate diagnosis and the prediction of developing of AD in its prodromal phase particularly within a 1 to 2 years of MCI onset, can help treat early and could minimize progression of the disease [35–38]. This is especially true in Atypical AD characterized by presentations of non-amnestic features of AD including predominant impairment in visual, language, executive, behavioral, and motor functions. These syndromes present as a young onset dementia, before age 65, and over half of these patients are misdiagnosed. It is probable that the early precise diagnosis of non-amnestic AD can reduce disease progression and morbidity and improve patients' quality of life. Therefore, it is remarkable that the biomarkers' role in the AD diagnosis is imperative [39].

Indeed, the clinical complexity of AD causes about 25% to 30% misdiagnosis when AD patients are assessed at memory clinics. The rate of misdiagnosis increases to 50% to 70% when AD patients are evaluated in the primary care and where the cognitive function tests are not routine. This high misdiagnosis rate is certainly due to a lack of accurate, accessible, and affordable diagnostic methods [40–42]. Moreover, numerous new therapeutic agents for AD therapies are undergoing clinical trials that are presumed to be effective in the earlier stages of the disease (MCI and mild AD), and two of them, antibody-based drugs, Donanemab and Lecanemab, have been approval by the U.S. Food and Drug Administration (FDA) [43,44]. The discovery of biofluid biomarkers over the last decade has significantly improved our knowledge of the evolving Alzheimer's pathological alterations. They have facilitated *in vivo* detection of AD pathologies, improved the diagnosis of AD phenotypes, and helped differentiate them from other types of neurodegenerative dementia [45]. The latest updated criteria of AD diagnosis by the Alzheimer's Association (AA) provided to a new diagnostic criterion for AD. An ATN profile (with β amyloid deposition, pathologic tau, and neurodegeneration) leads to a clinical and biological definition of AD [46]. In this regard, the AD biomarkers were classified into three major categories: fundamental biomarkers of AD core neuropathological features [47], nonspecific biomarkers involved in the pathogenesis of both AD and other degenerative disorders, and biomarkers of co pathology findings (Table 1). Core AD biomarkers include core 1 (Aβ 42, p-tau217,

Table 1. Classification of AD biomarkers.

Biomarker category	CSF or plasma	Imaging
Core Biomarkers		
Core 1		
A (Aβ proteinopathy)	Aβ 42	Amyloid PET
T1: (phosphorylated and secreted AD tau)	p-tau217, p-tau181, p-tau231	
Core 2		
T2 (AD tau proteinopathy)	MTBR-tau243, Other phosphorylated tau forms (e.g., p-tau205), non-phosphorylated mid-region tau fragments	Tau PET
Biomarkers ofnonspecificprocesses involved in AD pathophysiology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MRI, FDG PET
I (inflammation) Astrocytic activation	GFAP	
Biomarkers of non-AD co pathology		
V vascular brain injury		Infarction on MRI or CT, WMH
S α-synuclein	α-synuclein αSyn-SAA αSyn-SAA	

p-tau181, p-tau231 and amyloid PET) and core 2 such as microtubule-binding region (MTBR-tau243), other phosphorylated tau forms (e.g. p-tau205), non-phosphorylated mid-region tau fragments biomarkers and Tau PET. Core 1 biomarkers can identify the early stage and asymptomatic AD, but Core 2 biomarkers can not individually be used as an AD diagnostic test. In other word, an abnormal Aβ 42 or p-tau217 or amyloid PET is generally necessary for neocortical AD tauopathy and a tau positive biomarker phenotype without positive amyloid profile is not compatible with Alzheimer's diagnosis [48–50]. Hence, all available biomarker tests do not have adequate accuracy for acceptable diagnosis of DA, but specific Core 1 biomarkers (Table 2) can establish AD diagnosis. Amyloid PET, CSF Aβ 42/40, CSF p-tau 181/Aβ 42, CSF t-tau/Aβ 42, and plasma p-tau 217 or combinations of these are currently suitable biomarkers for AD diagnosis [46,51]

Biofluid biomarkers in AD

Accumulation of Aβ in the growing neuritic plaques in AD causes the selective reduction of Aβ42 from the CSF, while the Aβ40 is nearly unchanged. Therefore, the CSF Aβ42/Aβ40 ratio measurement is a reliable biomarker in detecting cerebral Aβ deposition. Similarly, Aβ42 depletion with a reduction of the Aβ42/Aβ40 ratio can be detected in the plasma. Several immunoprecipitation mass spectrometry (IP-MS) methods and immunochemical tests for the plasma Aβ42/Aβ40 measurement have been developed but its diagnostic accuracy is limited due to peripheral amyloid production. However, the immunoassays show lower diagnostic performance in detecting amyloid pathology than IP-MS. The small range of alteration of plasma Aβ42/Aβ40 between individuals with positive Aβ and negative Aβ (8%–15%) compared to larger reduction of Aβ42/Aβ40 in CSF (40%–60%) is a crucial problem with testing of plasma Aβ42/Aβ40. In addition, Aβ is also produced in extracerebral tissues, which are not affected by brain Aβ pathology, and the plasma Aβ42/Aβ40 reduction is not completely correlated with brain Aβ pathology. Consequently, plasma Aβ42/Aβ40 is less sensitive than CSF Aβ42/Aβ40 in the detection of cerebral amyloidosis associated with AD, while the CSF Aβ42/Aβ40 ratio is a robust more accurate in AD diagnosis. Another noticeable characteristic of the Aβ42/Aβ40 ratio is that their levels are altered in the preclinical stages of AD. They can identify Aβ pathology with high accuracy in both individuals with unimpaired cognition and patients with MCI [39,42,46,52]. For showing the pattern and density of AD neuropathology in the brain, positron emission tomography (PET), molecular imaging technique, with different radiotracers has been utilized (Amyloid and Tau PET) [53,54]. Amyloid PET exhibits remarkable sensitivity in detecting AD [55–57] and can prognosticate future cognitive impairment over long follow-up periods [13,58] as a result of the significant delay between amyloid deposition and clinical findings [59]. Tau PET is the second neuropathological biomarker, though its clinical implementation is still limited. In research settings, it can accurately differentiate AD cases from controls and illustrate the spatial and temporal correlation with clinical presentations of AD [60–63]. Moreover, tau PET has been positive in 3R and 4R taupathies, however, compared to AD, its ability to differentiate these forms of taupathies from control individuals is less clear [64,65]. Several studies have shown that neocortical signals on tau PET are highly prognostic for the clinical progression of the AD continuum [66]. While PET has been used as a diagnostic technique for both amyloid and tau pathologies in research studies, recent evidence suggests that it can use, as a single diagnostic test, to verify both amyloid and tau pathologies [67]. Both PET and CSF biomarkers have already been approved by the FDA for AD diagnosis, however, invasiveness, accessibility, cost, and availability restrict their use in clinical practices.

Furthermore, the ultrasensitive techniques such as the Single-molecule Array (Simoa) have facilitated the early detection of biomarkers, such as ptau, in the plasma with high sensitivity. These emerging technologies and novel neurodegenerative biomarkers in the simple Blood-based test offer a unique advantage to use them in clinical testing and drug development trials [68]. So far, several very sensitive plasma p-tau assays for measurement of AD biomarkers including p-tau 181, p-tau 217 and p-tau 231 have been established [42] using specific antibodies against the N-terminus or mid-domain of the tau protein in biofluids [69]. Studies of autopsy confirmed case have shown that plasma p-tau181 concentrations are correlated with both the Aβ plaques density and tau tangles and it can differentiate AD cases from other forms of

Table 2. Intended uses for imaging, CSF, and plasma biomarker assays.

Diagnosis Intended use	CSF	Plasma	Imaging
A: (Aβ proteinopathy)	—	—	Amyloid PET
T1: (phosphorylated and secreted AD tau)	—	p-tau217	—
Hybrid ratios Staging,	p-tau181/Aβ42, t-tau/Aβ42, Aβ42/40	%p-tau217	—

dementia. It also can distinguish AD from other tauopathies such as primary age-related tauopathy, progressive supranuclear palsy, corticobasal degeneration and Pick's disease [70,71]. In addition, a number of clinical studies have shown that plasma p-tau181 can accurately separate AD from other neurodegenerative diseases [15,72,73]. However, different plasma p-tau species reflect the different stages of AD pathological cascade. While p-tau231 represents the earliest increases in Aβ accumulation, p-tau217 is strongly correlated with both brain amyloidosis and early tau toxicity [74,75]. The tau microtubule-binding region containing residue 243 (MTBR- tau 243) selectively reflect tau pathology whereas other tau species including p-tau181 are reflecting tau pathology in the later stages AD [74,75]. Plasma p-tau217, the same as p-tau 181, can differentiate pathologically confirmed AD cases from non-AD cases. It also can distinguish between AD and other tauopathies [15,76,77] Although plasma concentrations of all ptau forms are higher in AD compared to other non-AD dementia, the plasma p-tau217 has the highest levels [77–79] In addition, plasma p-tau217 starts to change earlier than other p-tau variants, and it shows an increase during both the preclinical and prodromal stages of AD. Hence, plasma p-tau217 can predict upcoming cognitive deterioration in the AD continuum [80,81].

Moreover, with the knowledge regarding the new disease modifying treatments and the use of plasma p-tau217 in screening and diagnosis of AD, it is time to settle a reliable lab diagnostic immunoassay for measuring plasma p-tau217. Several longitudinal and cross-sectional studies using amyloid and tau PET, have demonstrated an evident correlation between plasma p-tau, particularly p-tau217 levels and AD core pathologies across the disease continuum [82,83]. Although p-tau biomarkers are expected to be an indicator of tau pathology, several observational studies provide evidence that concentrations of p-tau are closely correlated with Aβ deposition [79,83]. Accordingly, plasma p-tau217 exhibited high performance for abnormal statuses of Aβ PET and tau PET which were equivalent to those of CSF biomarkers [84–86]. While many of these studies focus on PET Aβ+ or Aβ− based on visual reads of scans or specific thresholds on PET Centiloids (CL), in a large cohort study, the diagnostic performance of plasma Aβ42/Aβ40 ratio, p-tau217 ratio, and the combination of both were evaluated in predicting amyloid status across a range of CL thresholds (15 -90) in two independent cohorts including cognitively unimpaired (CUI), MCI and mild AD [87]. They continuously showed that p-tau217 ratio had an excellent performance, with high AUC and specificity at almost every CL threshold, but the best overall performance was observed at the CL > 50 with an approximate AUC of 0.94 and specificity of 93%.

Analytical and clinical performance of plasma p-tau217

Plasma p-tau217 demonstrated better performance compared to other p-tau species in distinguishing AD from non-AD dementia and detecting AD pathology in MCI patients [17,77]. In a head-to-head comparison of plasma and CSF tau immunoassays, Ashton et al. found that plasma p-tau217 shows the sturdiest correlation with cross-sectional and longitudinal changes in Aβ pathology, likely due to a more prominent and persistent rise in symptomatic cases [88]. Additionally, p-tau217 indicates the direction of the disease course, with its increasing levels aligned with declining cognitive function and worsening brain atrophy related to elevated Aβ pathology [89]. Despite the promising potential of plasma p-tau217 as a diagnostic biomarker for AD, its widespread analysis was impeded by the limited availability of commercial assays. Furthermore, with recent advances in AD-modifying therapies and the importance of early Alzheimer's diagnosis, the need for a reliable plasma p-tau217 immunoassays in clinical laboratories have increased. Several immunoassays such as the Lilly assay utilized Meso Scale Discovery Electrochemiluminescence platform (MSD ECL) platform and the Janssen SIMOA immunoassay using the Quanterix HD-X platform were developed to quantify plasma p-tau217. These are in-house research-use assays, utilizing privately developed antibodies, and are not available for clinical practice, however, Groot et al. in a study consisting of two cohorts, compared these two immunoassays head-to-head [86]. They compared these two assays by their assessed the Receiver Operating Characteristic (ROC) analyses using a cohort including 27 healthy controls and 25 MCI cases, and a cohort of 147 MCI patients who have been followed for 4.92 years. Both assays had similar performance in identifying Aβ status in CSF, differentiating MCI from controls, and predicting the transformation from MCI to AD (Table 3). Additionally, both methods showed similar correlations with baseline and annual changes in MMSE scores, and there was strong concordance between the two immunoassays in both cohorts, with strong diagnostic and prognostic results [86]. In another study, Kivisäkk et al. measured p-tau217 in plasma from 131 AD cases (confirmed by CSF biomarkers) and 70 controls utilizing a p-tau217 S-PLEX® assay developed by Meso Scale Discovery (MSD; Rockville, MD). The assay demonstrated excellent performance in

Table 3. Comparison of the accuracy different platforms for measurement of plasma p-tau217.

	Platform	Clinical stages	Threshold (pg/L)	AUC	Specificity	Sensitivity	PPV	NPV
Groot, C. [86]	Janssen	Controls, MCI, MCI to AD	–	0.91	–	–	–	–
Palmqvist, S. [77,17]	Eli Lilly	AD vs. other NDD[a]	–	0.96-0.99	86 – 92	93	–	–
Ashton,N. J. [82,83]	Janssen			0.96				
	Lilly			0.94				
Kivisäkk, P. [78]	MSD S-PLEX[b]	AD vs. controls	–	0.98	–	–	–	–
Ashton,N. J. [76]	ALZpath	Preclinical to MCI	Binary: >0.42	0.92–0.96	74.5–85.1	85.0–98.2	48 – 85	77.6–97.7
			<0.40 (negative), >0.63 (positive)	0.93–0.97	94.1–98.6	86.7–98.2	87.5 – 98.5	88.5 – 98.4
Arranz, J. [90]	Lumipule	Controls, MCI, MCI to AD	0.130	0.92-0.97	97.8%	65.5%	96.9%	73.1%
			0.186		95.0%	82.1%	94.4%	83.5%
			0.247		90.6%	89.7%	90.9%	89.4%
			0.388		69.8%	95.2%	76.7%	93.3%
Zhong X [84–86]	Lumipulse	Normal, MCI, AD		0.94 – 0.97				
Pilotto A [85]	Lumipulse	MCI, Mild AD	0.291	0.952	–	–	–	–
	ALZpath		0.542	0.955				
Janelidze, S. [17]	WashU	MCI-AD	–	0.947	90.6	94.4	–	–
	Lilly	Non-progressors A–		0.886	84.4	85.9		
	Janss	Non progressors A+		0.858	87.5	87.5		
Figdore DJ [91]	ALZPath	MCI, AD	0.91	–	84	84	-	-
	Lumipulse		0.93		86	88	-	-
Frykman H. [93]	ALZpath	Neuropathology confirmed cases and plasma and CSF matched cases	0.34	0.94	67.4	95.8	83.1	90.6
	Lumipulse		0.40	0.94	76.7%	87.5%	86.3%	78.6%
			0.63	0.94	95.3%	79.2%	96.6%	73.2%
			0.13	0.90	46.5%	96.6%	71.3%	90.9%
			0.18	0.90	67.4%	88.1%	78.9%	80.5%
			0.37	0.90	93.0%	67.8%	93.0%	67.8%

[a]Neurodegenerative Disorders.
[b]Developed by Meso Scale Discovery using a sandwich immunoassay format using monoclonal antibodies and electrochemiluminescence.

detecting plasma p-tau217, with a lower limit of quantification (LLOQ) of 1.84 pg/mL and intra/inter-plate coefficients of variation (CVs) of 5.5% (0.3–15.0%) and 5.7% respectively. In addition, the plasma p-tau217 assay differentiates AD cases from healthy controls with 3.9-fold higher concentrations in AD cases (Table 3) [78]. More recently, the ALZpath p-tau217 assay, a SIMOA immunoassay for use on the Quanterix HD-X platform, has been available commercially. A recently published study demonstrated that the efficacy of the plasma ALZpath p-tau217 immunoassay in accurately diagnosing AD is comparable to that of CSF biomarkers and PET [76]. This study included three cohorts with a total of 786 participants, both normal and impaired cognitive function, classified by amyloid and tau status using PET or CSF biomarkers. The ALZpath p-tau217 immunoassay was highly accurate in identifying elevated Aβ and tau pathology across all cohorts, which was similar to CSF biomarkers accuracy in detecting abnormal PET signals (Table 3). Additionally, based on a three-level reference for identifying Aβ pathology, it provided consistent results and lowered the need for verification testing by about 80%. Moreover, this study determined consistent cutoffs across three cohorts to detect longitudinal change of plasma p-tau217, particularly at the preclinical and early stages of AD. They also showed an annual increase of plasma p-tau217 concentrations in only Aβ-positive individuals, with the highest rise detected in cases with abnormal tau pathology [76]. Recently, Fujirebio, which had implemented a fully automated platform (Lumipulse G instrument) to quantify CSF AD biomarkers in clinical laboratories, launched assays to measure p-tau217 in plasma. In a study, using LUMIPULSE platform, Arranz et al. analyzed 290 plasma samples from consecutive participants, including 66 cognitively unimpaired individuals, 130 with MCI, and 94 with dementia [90]. The amyloid-positive cases had higher plasma p-tau217 and p-tau181 levels compared to amyloid negative individuals, however, plasma and CSF p-tau181 and the Aβ1–42/Aβ1–40 ratio indicated a moderate correlation. The AUC for discriminating participants with amyloid pathology was 0.94 (95% CI 0.92–0.97) and 0.88 (95% CI 0.84–0.92) for plasma p-tau217 and both plasma p-tau181 and the Aβ1–42/Aβ1–40 ratio respectively. In addition, the performance of plasma p-tau217 was high across different clinical diagnosis categories with an AUC = 0.97 in differentiating cognitively unimpaired from AD, AUC = 0.92 to differentiate amyloid positive from amyloid negative MCI group and AUC = 0.95 to differentiate Amyloid positive patients with dementia from different Amyloid

negative neurodegenerative or non degenerative dementia [90]. In another study, Zhong et al. quantified plasma p-tau217, p-tau181, Aβ1-40, Aβ1-42, and neurofilament light chain in a research project involving 260 voluntary participants with plasma samples and amyloid PET and a real-world experience including 100 consecutive participants with plasma and CSF samples. They classified all participants by brain amyloid status using FDA/European Medicines Agency–recommended methods for CSF biomarkers and PET signals. Plasma p-tau217 and p-tau217/Aβ1-42 ratio showed higher accuracy in detecting brain Aβ pathology (Table 3). Plasma biomarkers demonstrated excellent correlations with their CSF counterparts and with PET signals and showed significant associations in individuals with amyloid-positive findings (Table 3) [84]. In another recent study, Pilotto et al. in a head-to-head comparison, evaluated the performance of Lumipulse and ALZpath SIMOA for detecting plasma p-tau217 in AD patients. They measured plasma p-tau217 in 392 participants, including 162 with AD, 70 with other neurodegenerative diseases who had CSF biomarkers values, and 160 controls. Both techniques potentially differentiate AD from non-AD neurodegenerative diseases and controls, with high stability, and similar correlations to CSF p-tau181 levels. Both assays demonstrated roughly a similar accuracy for distinguishing AD from non-AD and controls [85]. In another recent study, Figdore et al. assessed the cutoffs for the ALZpath and Lumipulse plasma p-tau217 immunoassays in samples from patients with clinically diagnosed MCI and mild AD determined by amyloid PET. The study, similar to previous studies, suggested a two-cut points approach for clinical selection of AD cases to minimize potential false-positive results and improve diagnostic accuracy. While with one-cut point consideration, neither assay reached to sensitivity and specificity ≥ 90%, by two-cutoffs approach, a 92% and 96% sensitivity and specificity were obtained. However, inconclusive results were found in 39% of the ALZpath assay and 22% of the Fujirebio assays [91]. Furthering to evaluate the clinical application of ALZpath plasma p-tau217 by SIMOA and Lumipulse p-tau217 immunoassays, as a laboratory diagnostic test (LDT), we assessed their diagnostic performance compared to CSF amyloid Aß42/40 ratio and p-tau181, as well as pathology confirmed diagnosis. In this regard, we conducted a comprehensive analytical and clinical validation study using 360 samples of amyloid PET-negative healthy individuals [92], 115 samples of neuropathology-confirmed cases with an averaged age, and 55 matched CSF and plasma samples [93]. Moreover, to determine the cutoffs for AD clinical diagnosis, we compared two methods against CSF biomarkers and autopsy findings. According to the determined reference ranges for ALZpath p-tau217(<0.40 ng/L and >0.63 ng/L) [76], the assay specificity at the 0.63 ng/L threshold was consistently high (Table 3) suggesting this cutoff provides persistent results across cohorts to detect amyloid pathology. Moreover, the cut point of the 0.40 ng/L demonstrated $a < 90\%$ sensitivity for amyloid pathology, defined by both CSF Aβ 42/40 ratio and autopsy, however, a 0.34 ng/L cutoff exhibited a sensitivity of approximately 96% and 93% for the autopsy-confirmed and CSF cohorts, respectively. On the other hand, a specificity of approximately 88% at 0.63 ng/L and a sensitivity of about 93% at 0.34 ng/L were obtained with tau pathology verified by CSF p-tau181. Moreover, the Fujirebio p-tau217 assay verified unique thresholds with an approximate 97% sensitivity at 0.13 ng/L threshold, and 93% specificity at 0.37 ng/L cutoff. According to CSF Aβ 42/40 ratio, its sensitivity was about 88% at the lower cut point with an approximate 95% specificity at the upper cutoff. In addition, a 0.18 ng/L binary reference threshold showed an approximate 67% and 88% specificity and sensitivity for the neuropathological samples, and about 95% and 81% specificity and sensitivity for the CSF samples, with the resembling results for tau pathology (Table 3).

Additionally, to address predictive values as an essential for interpreting personalized test results, Therriault et al. evaluated the PPV and NPV of plasma p-tau217 for amyloid-β pathology in relation to patient age and AD clinical phenotypes by analyzing data from 6,896 individuals across 11 cohorts in six countries [94]. They demonstrated that plasma p-tau217 could reliably confirm Aβ pathology in patients with clinically probable AD dementia with a PPV exceeding 95%. The researchers also found that in MCI cases, the interpretation of plasma p-tau217 results varied with patient age, and PPVs of plasma p-tau217 increased with age, reaching 92.5% for individuals aged 90 years. On the other hand, they showed that NPVs for Aβ pathology rise above 90% for individuals younger, which means negative plasma p-tau217 results effectively ruled out Aβ pathology in non-AD dementia syndromes, with high NPV values.

In conclusion, measurement of AD biomarkers will be a key factor in determining eligibility for disease-modifying therapy in clinical practice. Plasma p-tau 217 is a robust biomarker for diagnosis and monitoring of AD and it has demonstrated high efficacy in identifying Aβ pathology with levels in blood also being associated to clinical progression, making it a feasible test for AD screening in clinical practice. Several assays, including the ALZpath p-tau217 assay and the Fujirebio

plasma p-tau217 assay, have been made commercially available for research use. Numerous studies (Table 3), including ours, have evaluated these plasma p-tau immunoassays as laboratory-developed tests, reinforcing the clinical utility of plasma p-tau217 in AD diagnosis and highlighting differences in the performance of current plasma p-tau217 immunoassays for clinical use. In conclusion, plasma p-tau217 is a front-runner biomarker for AD diagnosis, however, for establishing its diagnostic value, conducting prospective studies in the real-world memory clinics is crucial to define a precise diagnostic cutoff value and reference standard. Additionally, prospective clinical validation studies focused on plasma p-tau217 are crucial for enhancing its diagnostic accuracy and ensuring its results consistency. As AD biomarkers are known to be influenced by risk factors of AD and other covariates such as renal disease [95], to confidently interpret plasma p-tau217, particularly in preclinical stage of AD, prospective, community- based studies are needed to address its variability and to establish a certain diagnostic cutoff. Such studies could also enhance the accuracy of biological diagnosis of AD and help characterize plasma p-tau217 levels across AD continuum.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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