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RESEARCH ARTICLE

Clinical decision points for two plasma p-tau217 laboratory developed tests in neuropathology confirmed samples

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Abstract

INTRODUCTION: We evaluated the diagnostic performance of two commercial plasma p-tau217 immunoassays compared to cerebrospinal fluid (CSF) testing and neuropathology.

METHODS: One hundred and seventy plasma samples from the University of British Columbia Hospital Clinic for Alzheimer's (AD) and Related Disorders were analyzed for p-tau217 using Fujirebio and ALZpath assays. Decision points were determined using CSF testing and autopsy findings as the standard.

RESULTS: Fujirebio and ALZpath p-tau217 had similar overall analytical and clinical performance, with distinct decision points for each assay. Based on autopsy findings, both p-tau217 assays identified individuals with AD from other neurodegenerative diseases (ALZpath area under the curve [AUC] = 0.94, Fujirebio AUC = 0.90). The ALZpath assay detected AD pathology at milder disease stages compared to the Fujirebio assay.

DISCUSSION: Our study reinforces the clinical utility of plasma p-tau217 as an AD biomarker. Differences in test performance and clinical decision points suggest an assay-specific diagnostic approach is required for plasma p-tau217 in clinical practice.

KEYWORDS

Alzheimer's disease, CSF Aβ 42 to 40 ratio, CSF p-tau181, immunoassays, neuropathology diagnosis, plasma p-tau217

Highlights

- Two commercially available p-tau217 immunoassays (ALZpath and Fujirebio) showed equal performance based on CSF testing.
- ALZpath p-tau217 showed higher performance compared to Fujirebio p-tau217 based on AD diagnosis by neuropathology confirmation.
- Specific plasma p-tau217 assays may require distinct decision points for AD screening, diagnosis, and disease progression monitoring.

1 | BACKGROUND

While invasiveness, accessibility, cost, and availability limit the use of positron emission tomography (PET) and cerebrospinal fluid (CSF) biomarkers in clinical practices to diagnosis Alzheimer's disease (AD), developing novel immunoassay technologies has facilitated the early detection of biomarkers such as phosphorylated tau (p-tau) in plasma. Large clinical-based studies have shown that plasma p-tau217 can distinguish AD from other neurodegenerative diseases with high diagnostic accuracy. Moreover, plasma p-tau217 is an accurate marker to predict the future development of AD in symptomatic patients with either mild cognitive impairment (MCI) or subjective cognitive decline, due to its large increase in the earlier stage of AD.[1–3]

With the emerging new AD-modifying treatments and the role of plasma p-tau217 in Alzheimer's diagnosis, it is crucial to establish a reliable immunoassay for measuring plasma p-tau217 in the clinical laboratory. The ALZpath and Fujirebio p-tau217 assays were recently developed for measuring plasma p-tau217, and are currently being used by national laboratories as clinical assays without United States Food and Drug Administration (FDA) approval.[4–6] The ALZpath and Fujirebio assays use unique ultrasensitive methods to detect low-abundance proteins in plasma. The ALZpath assay uses a digital immunoassay (SIMOA), without the need for signal amplification. In contrast, the Fujirebio assay uses a chemiluminescent enzyme immunoassay (CLEIA), which amplifies the signal to detect low-abundant proteins.

We further the work of recent head-to-head studies evaluating the diagnostic accuracy of ALZpath and Fujirebio plasma p-tau217 assays in clinically diagnosed AD,[7,8] we assessed the diagnostic performance of both assays in comparison to FDA -approved CSF testing for amyloid Aß42/40 ratio and p-tau181, as well as postmortem neuropathological evaluation of cases who had paired plasma samples at diagnosis of dementia.

RESEARCH IN CONTEXT

1. **Systematic review**: Several studies have suggested plasma p-tau217 is a robust biomarker for Alzheimer's disease (AD) diagnosis and monitoring its progression. However, the majority of p-tau217 tests are intended for research purposes and are not widely available for clinical testing.
2. **Interpretation**: We assessed the analytical and clinical performance of two laboratory-developed p-tau217 immunoassays, ALZpath p-tau217 and Fujirebio p-tau217, compared to cerebrospinal fluid (CSF) AD biomarkers and neuropathology from autopsy findings. Both assays showed excellent clinical performance, but ALZpath exhibited better results, with an area under the curve (AUC) value of 0.94 compared to Fujirebio's AUC value of 0.90, in the neuropathology-confirmed cohort.
3. **Future directions**: Our study provides a comprehensive analysis of available plasma p-tau217 assays before wider implementation in clinical practice. These two methodologies may have different thresholds for screening, diagnosis, and monitoring of disease progression and therapy, highlighting the need for standardization across laboratory and testing methods.

2 | METHODS

2.1 | Study population

Participants were recruited from the University of British Columbia Hospital Clinic for Alzheimer's and Related Disorders (UBCH-CARD) in Vancouver, Canada. 155 subjects had post-mortem neuropathology evaluation, and an additional 55 subjects had CSF collected, all subjects had plasma samples at the time of the study. Patients are assessed by specialty-trained neurologists and geriatricians who have expertise in dementia assessments. After an initial detailed evaluation, patients are clinically diagnosed with AD, based on NIA-AA criteria or other established clinical diagnosis criteria.[9]

2.2 | Plasma and CSF sampling

Venous blood (K2 EDTA) and CSF (polypropylene tubes) collection occurred within 4 h using Alzheimer's Disease Neuroimaging Initiative (ADNI) biobanking procedures. All CSF and plasma samples were blinded and randomized before being evaluated. Plasma p-tau217 was measured using ALZpath Simoa p-tau217 v2 (Quanterix, MA, USA) on the Quanterix HD-X Analyzer platform in duplicate and Lumipulse G p-tau217 (Fujirebio Europe N.V., Belgium) on the Lumipulse G1200 platform in singlicate. For the ALZpath assay, three internal quality controls were used and all values were within ± 15% of established ranges. For the Fujirebio assay, two external quality controls were used and ran within manufacturer-specified ranges. CSF Aβ 42 to 40 ratio and p-tau181 levels were measured using Lumipulse G β-Amyloid 1-40, Lumipulse G β-Amyloid 1-42, and Lumipulse G p-tau181 kits (Fujirebio Europe N.V., Belgium) on the Lumipulse G1200 platform.

2.3 | Analytical validation of the p-tau217 assays

The analytical validation of both p-tau217 immunoassays was performed by Neurocode at their CLIA-licensed facility. Sensitivity (including the limit of blank [LoB], limit of detection [LoD], and lower limit of quantification [LLoQ]), precision, linearity, interference, and sample stability were validated in accordance with methods established by the Clinical and Laboratory Standards Institute (CLSI). LoB, LoD, and LLoQ were determined following CLSI EP17-A2E using two reagent lots. The ALZpath p-tau217 had a LoB of 0.0035 ng/L, LoD of 0.0074 ng/L, and LLoQ of 0.032 ng/L. The Fujirebio p-tau217 had a LoB of 0.04 ng/L, LoD of 0.052 ng/L, and LLoQ of 0.06 ng/L. A precision profile plot was used to determine LLoQ, based on two reagent lots and a 20% coefficient of variation.

Precision was assessed according to CLSI EP05-A3 using two reagent lots. Linearity was evaluated per CLSI EP06-A. Interference testing followed CLSI EP07-A3. Sample stability for each assay was determined following CLSI EP25-A by measuring samples stored at room temperature, 4^0C, -20^0C, and -80^0C.

2.4 | Neuropathology evaluation

Autopsies were performed at UBC on patients who were referred from UBCH-CARD with informed consent. Formalin-fixed, paraffin-embedded brain tissue blocks were cut at 5 microns and stained with hematoxylin and eosin (HE), HE combined with Luxol fast blue, modified Bielschowsky silver, Gallyas silver, and Congo red stains. Standard immunohistochemistry was performed using the Dako Omnis automated staining system with primary antibodies against alpha-synuclein (α-syn) (clone LB509 Invitrogen Cat#180215; 1:10,000), beta-amyloid (clone 6F/3D; DAKO Cat#MO8720; 1:100), hyperphosphorylated tau (clone AT-8; Thermo Fisher Cat#MN1020; 1:2000), and phosphorylation independent TDP-43 (ProteinTech polyclonal Cat#10782-2-AP; 1:1000), and ubiquitin (DAKO polyclonal Cat#Z0458; 1:500).

2.5 | Statistical analysis

Statistical analysis was performed in R (version 4.3.1). Accuracy and clinical decision point analysis were performed using receiver operating characteristic (ROC) curves generated using the R package pROC. Delong's test for two correlated ROC curves was used to compare test performance. Linear correlation was determined using either Spearman's or Pearson's correlation test depending on the sample distribution. A comparison of two sets of variables was conducted using Welch's two-sample *t*-test. For three or more normally distributed continuous variables, analysis of variance (ANOVA) was used followed by a pair-wise comparison using Tukey's honestly significant difference (HSD) test.

TABLE 1 Characteristics of the CARD NP and CSF cohorts.

Characteristic	Mean (SD)	
	NP CARD ($N = 115$)	CSF CARD ($N = 55$)
Age, years[a]	71.8 (11.9)	67.2 (10.4)
Sex, no. (%)		
Female	54 (47.0)	27 (49.1)
Male	61 (53.0)	28 (50.9)
APOE ε4 carriers, no. (%)	57 (49.6)	21 (47.7)[b]
Diagnosis, no. (%)[c]		
AD only	30 (26.1)	21
AD with CAA	7 (6.1)	–
AD with DLB	13 (11.3)	1
AD with vascular	7 (6.1)	–
AD with mixed pathologies	13 (11.3)	4
MCI	–	13
NCI	–	2
TDP-43 only	18 (15.7)	–
Synuclein only	4 (3.5)	–
Tau only	18 (15.7)	1
other non-AD	5 (4.3)	13
CSF Aβ 42/40, pg/mL	–	0.063 (0.025)
CSF p-tau181, pg/mL	–	63.4 (37.4)
Plasma p-tau217 (ALZpath), pg/mL	0.91 (0.74)	0.83 (0.76)
Plasma p-tau217 (Lumipulse), pg/mL	0.54 (0.58)[d]	0.44 (0.49)[e]

Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; CAA, cerebral amyloid angiopathy; CSF, cerebrospinal fluid; DLB, dementia with Lewy bodies; MCI, mild cognitive impairment; NCI, no cognitive impairment; NP, neuropathology.

[a]Age refers to age at death for the neuropathy cohort and age at fluid biomarker collection for the CSF cohort.

[b]$N = 44$ samples with APOE genotyping.

[c]Diagnosis refers to the final diagnosis for the neuropathy cohort and clinical diagnosis for the CSF cohort.

[d]Insufficient volume for testing in a subset of plasma samples, $N = 102$.

[e]Insufficient volume for testing in a subset of plasma samples, $N = 51$.

3 | RESULTS

3.1 | Analytical performance of two p-tau217 plasma immune assays

ALZpath and Fujirebio p-tau217 assays were validated as laboratory-developed tests based on CLSI guidelines at the Neurocode laboratory. All samples measured above the limit of detection for both assays. Intra-laboratory coefficient of variation was assessed for each assay using three concentration levels (low, medium, and high) (Figures S1,2). Sample stability and interference were similar between the two plasma p-tau217 assays, though moderate heterophilic antibodies interference and reduced frozen sample stability after three freeze-thaw cycles were observed for the Fujirebio assay (Figures S1,2).

3.2 | Study participant clinical characteristics

A total of 170 participants were included in this study. All participants had plasma samples collected, 55 had corresponding CSF samples, and a distinct cohort of 115 had brain autopsy examinations by a neuropathologist. Amyloid and tau-negative subjects had a mean CSF Aβ 42/40 ratio of 0.092 ± 0.010 and CSF p-tau181 concentration of 28.4 ± 10.0 pg/mL. Amyloid and tau-positive subjects had a mean CSF Aβ 42/40 ratio of 0.045 ± 0.010 and a mean CSF p-tau181 concentration of 90.0 ± 28.7 pg/mL (Table S1). The final diagnosis of the neuropathology subgroup was a mixture of pure AD, AD with mixed pathology, and non-AD dementia (Table 1).

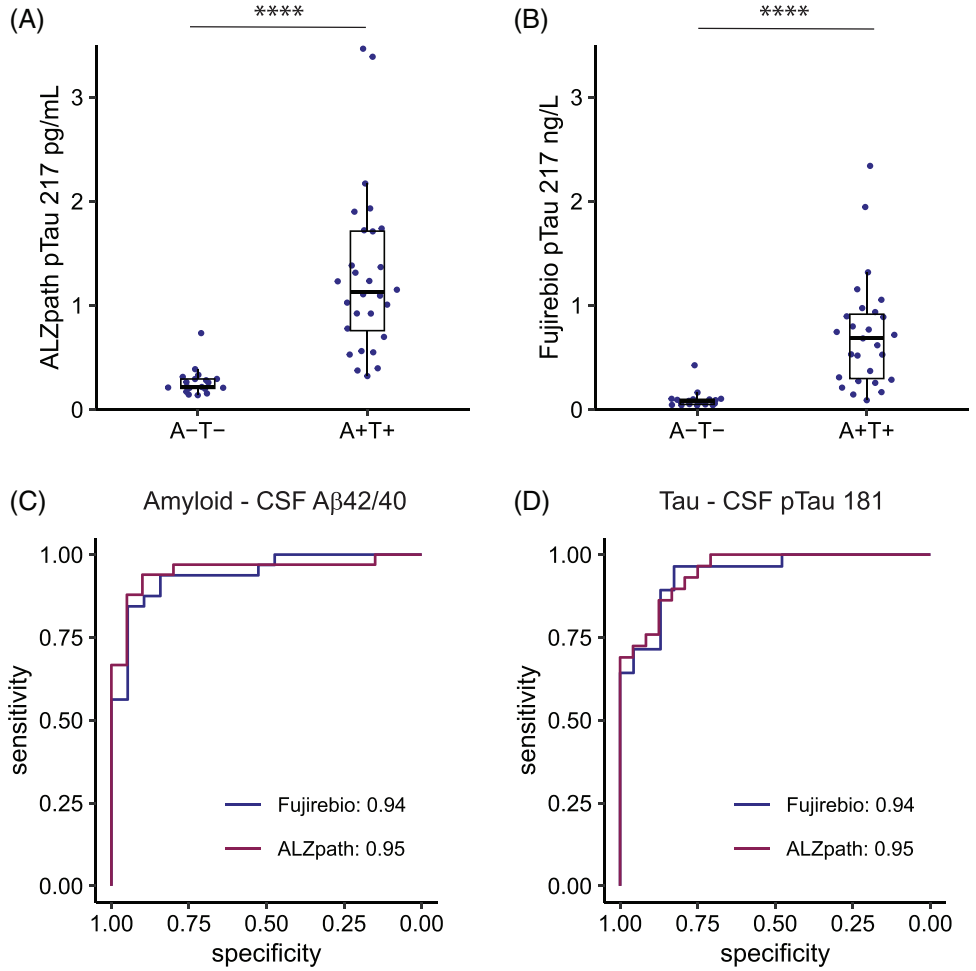

FIGURE 1 ALZpath and Fujirebio plasma p-tau217 assays have comparable clinical performance to CSF Aβ 42/40 and p-tau181 biomarkers. (A, B) The p-tau217 concentration by AT profile for UBC CARD CSF cohort. (A) ALZpath and (B) Fujirebio p-tau217 showed significantly increased concentrations in the A+T+ group, *p*-value < 0.0001. (C) ROC curve comparisons for plasma p-tau217 immuoassays compared to CSF Aβ42/40. (D) ROC curve comparisons for plasma p-tau217 immuoassays compared to CSF p-tau181. CSF, cerebrospinal fluid; p-tau, phosphorylated tau; ROC, receiver operating characteristic; UBC CARD, University of British Columbia Hospital Clinic for Alzheimer's and Related Disorders.

3.3 | Comparison of p-tau217 plasma assays to CSF amyloid and tau biomarkers

The p-tau217 concentrations of both plasma assays were significantly increased in the amyloid and tau positive (A+T+) group compared to the A-T- group (Figure 1A,B). Amyloid positivity was determined by a CSF Aβ42/40 ratio of less than 0.073, and tau positivity was determined by CSF p-tau181 levels > 50.2 pg/mL. This is consistent with other studies of amyloid and tau pathology for ALZpath and Fujirebio.[10,11] Encouragingly, both ALZpath and Fujirebio p-tau217 assays had very high correlation with both CSF amyloid (ALZpath: AUC 0.95; 95% CI: 0.89–1.00, Fujirebio: AUC 0.94 [0.88–1.00]) and tau status (ALZpath: AUC 0.95 (0.90–1.00), Fujirebio: AUC 0.94 (0.88–1.00)) (Figure 1C,D). Specifically, plasma p-tau217 correlates negatively with CSF Aβ 42/40 levels and positively with CSF p-tau181 for both ALZpath and Fujirebio (Figure S3). There was no significant difference in the performance of the two p-tau217 assays in predicting amyloid or tau abnormality compared to CSF.

3.4 | Diagnostic performance of plasma p-tau217 to identify autopsy-verified AD pathology from non-AD disorders

Using a pathological diagnosis as the gold standard, the ALZpath plasma p-tau217 assay outperformed the Fujirebio assay for predicting autopsy-verified AD pathology, with a significantly higher AUC of 0.94 compared to 0.90 (*p*-value 0.023) (Figure 2A). For both platforms, plasma p-tau217 levels were significantly higher in autopsy-verified pure AD compared to AD with mixed disease pathology (*p*-value < 0.001 Figure 2B; *p*-value < 0.0001 Figure 2C) or non-AD disorders (*p*-value < 0.0001; Figure 2B,C). Moreover, the mixed AD cohort had significantly higher p-tau217 levels compared to non-AD disorders across both platforms (*p*-value < 0.0001 Figure 2B; *p*-value < 0.001 Figure 2C). However, the median fold difference between the non-AD group and AD with mixed pathology is lower for the Fujirebio assay at 2.42 compared to a 3.35-fold difference for ALZpath, whereas the median fold difference between non-AD dementia and pure AD was

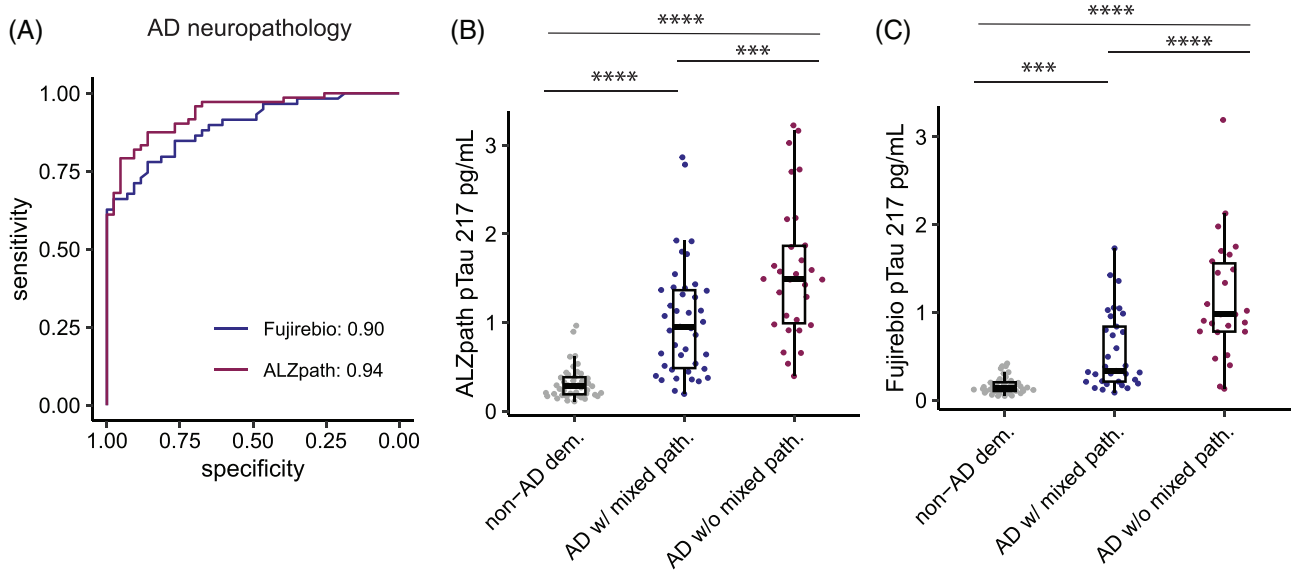

FIGURE 2 Comparison of ALZpath and Fujirebio plasma p-tau217 biomarker based on neuropathology. (A) ROC curve comparison for plasma p-tau217 immunoassays, Fujirebio AUC of 0.90, and ALZpath AUC of 0.94. (B, C) Pairwise comparison using Tukey's HSD test; ***p-value < 0.001 and ****p-value < 0.0001. (B) ALZpath p-tau217 levels in non-AD disease ($N = 43$), AD with mixed pathology ($N = 42$), and pure AD ($N = 30$). (C) Fujirebio p-tau217 levels in non-AD disease ($N = 43$), AD with mixed pathology ($N = 33$), and pure AD ($N = 26$). AD, Alzheimer's disease; AUC, area under the curve; HSD, honestly significant difference; ROC, receiver operating characteristic.

higher for the Fujirebio assay at 6.93-fold compared to the ALZpath assay at 5.29-fold. Patients with pure AD pathology or AD with cerebral amyloid angiopathy (CAA) had the highest levels of p-tau217, followed by AD with dementia with Lewy bodies (DLB) or vascular dementia. The lowest levels of p-tau 217 were observed in patients with a mixture of AD and at least two other pathologies associated with dementia. (Figure S4).

3.5 | Clinical decision points for plasma p-tau217 immunoassays

Separate decision points were set for the two p-tau217 tests based on the final diagnoses for the neuropathology cohort.[12] Reference ranges for ALZpath p-tau217 have been previously established as < 0.40 ng/L and > 0.63 ng/L.[10] The specificity at the higher established threshold of 0.63 ng/L was 95.3% (Table 2). However, the lower established threshold of 0.40 ng/L showed < 90% sensitivity for amyloid pathology determined by both CSF Aβ 42/40 ratio and neuropathology. A lower threshold of 0.34 ng/L had a sensitivity of 95.8% for the neuropathology cohort and 93.4% for the CSF cohort (Table 2). Within the intermediate zone (concentrations between 0.34 ng/L and 0.63 ng/L) 20.1% were within this range for the neuropathology confirmed cohort and 15.1% for the CSF cohort. For tau pathology determined by CSF p-tau181 the same reference ranges could be used.

Unique decision points were established for the Fujirebio p-tau217 assay. The lower threshold of 0.13 ng/L had 96.6% sensitivity and 90.9% negative predictive values, and the upper threshold of 0.37 ng/L had 93.0% specificity and 93.0% positive predictive values based on neuropathology (Table 3). These thresholds generate a larger intermediate zone compared to the ALZpath assay, with 32.2% of neuropathology cohort samples between 0.13 and 0.37, and 22.6% of the CSF cohort samples. A binary reference point is currently used by other clinical laboratories (0.18 ng/L) for this assay. For this decision point, we observed 67.4% specificity and 88.1% sensitivity for the neuropathology cohort and 94.7% specificity and 81.3% sensitivity for the CSF cohort (Table 3).

TABLE 2 ALZpath plasma p-tau217 cutoffs.

Amyloid pathology—CSF Aβ 42/40—AUC 0.95					
Threshold	**Spec.**	**Sens.**	**Acc.**	**PPV**	**NPV**
0.34	90.0%	93.4%	92.5%	93.9%	90.0%
0.40	95.0%	84.8%	88.7%	96.6%	79.2%
0.63	95.0%	72.7%	81.1%	96.0%	67.9%
Tau pathology—CSF p-tau181—AUC 0.95					
Threshold	**Spec.**	**Sens.**	**Acc.**	**PPV**	**NPV**
0.34	75.0%	93.1%	84.9%	81.8%	90.0%
0.40	83.3%	86.2%	84.9%	86.2%	83.3%
0.63	87.5%	75.9%	81.1%	88.0%	75.0%
Amyloid neuropathology—AUC 0.94					
Threshold	**Spec.**	**Sens.**	**Acc.**	**PPV**	**NPV**
0.34	67.4%	95.8%	85.2%	83.1%	90.6%
0.40	76.7%	87.5%	83.5%	86.3%	78.6%
0.63	95.3%	79.2%	85.2%	96.6%	73.2%

Abbreviations: Acc., accuracy; AUC, area under the curve; CSF, cerebrospinal fluid; NPV, negative predictive value; PPV, positive predictive value; Sens., sensitivity; Spec., specificity.

TABLE 3 Fujirebio plasma p-tau217 cutoffs.

Amyloid pathology—CSF Aβ 42/40—AUC 0.94					
Threshold	**Spec.**	**Sens.**	**Acc.**	**PPV**	**NPV**
0.13	84.2%	87.5%	86.3%	90.3%	80.0%
0.18	94.7%	81.3%	86.3%	96.3%	75.0%
0.37	94.7%	59.4%	72.5%	95.0%	58.1%
Tau pathology—CSF p-tau181—AUC 0.94					
Threshold	**Spec.**	**Sens.**	**Acc.**	**PPV**	**NPV**
0.13	82.6%	96.4%	90.2%	87.1%	95.0%
0.18	87.0%	85.7%	86.3%	88.9%	83.3%
0.37	95.7%	67.9%	80.4%	95.0%	71.0%
Amyloid neuropathology—AUC 0.90					
Threshold	**Spec.**	**Sens.**	**Acc.**	**PPV**	**NPV**
0.13	46.5%	96.6%	75.5%	71.3%	90.9%
0.18	67.4%	88.1%	79.4%	78.9%	80.5%
0.37	93.0%	67.8%	78.4%	93.0%	67.8%

Abbreviations: Acc., accuracy; AUC, area under the curve; CSF, cerebrospinal fluid; NPV, negative predictive value; PPV, positive predictive value; Sens., sensitivity; Spec., specificity.

3.6 | Plasma p-tau217 level and severity of AD by pathological staging

For both assays, the levels of p-tau217 increased according to Braak staging in the UBC-CARD neuropathology cohort. Plasma p-tau217 was significantly higher for individuals with Braak VI compared to individuals with other Braak stages (Figure 3A,B). The ALZpath assay p-tau217 measurement increase was apparent by Braak stage IV and was nearly significant by Braak stage V (p-value = 0.07 Braak V to 0, and p-value = 0.09 Braak V to I & II). This increase was less pronounced with the Fujirebio p-tau217 assay (Figure 3B).

We found that p-tau217 was significantly higher in individuals at Thal phase 4 (p-value < 0.05) and 5 (p-value < 0.0001) compared to phase 3 and below (Figure 3C, D). There was a significant difference between phases 4 and 5 with both the ALZpath and Fujirebio p-tau217 assays. A slight, but non-significant, increase was observed between phase 0 and phases 1–3 for the ALZpath assay (p-value > 0.05; 1.4 × fold change) (Figure 3C).

ALZpath p-tau217 was increased in individuals with moderate plaque score at CERAD stage 2 (p-value < 0.01) and a substantial increase by CERAD stage 3 (p-value < 0.0001) (Figure 3E). This increase was only observed at CERAD stage 3 with the Fujirebio p-tau217 assay (p-value < 0.0001) and was not significant at earlier plaque stages (Figure 3F). These results show that the level of plasma p-tau217 for both ALZpath and Fujirebio increased according to AD disease staging, with an increase observed at earlier disease staging with the ALZpath assay for both tau and amyloid pathology.

4 | DISCUSSION

This study provides a head-to-head comparison of the ALZpath and Fujirebio immunoassays for clinical use as laboratory-developed tests for plasma p-tau217. By using pathology-confirmed cases as a gold standard, for the clinical validation, we showed that the sensitivity of the ALZpath assay in the diagnosis of AD is higher than that of the Fujirebio assay at the lower reference value for both assays. We speculate that patients who have additional neurodegenerative disease pathologies may require less severe amyloid and tau pathology to exhibit dementia symptoms and were therefore lower p-tau217 levels.

There are a few recent publications that clinically validated plasma p-tau217 assays.[3,4,10,13] Similar cutoff points were observed for the Fujirebio p-tau217 assay compared to our study. For the ALZpath p-tau217, however, the upper cut-point was significantly higher for Figdore et al. at 0.92 pg/mL compared to 0.63 pg/mL determined by our study and several other studies. The reason for this discrepancy is unclear but may be due to how amyloid status was determined for the study cohort or reagent problems. This suggests further revaluation of the cut-points for both assays is required before widespread clinical implementation.

We observed differences in the analytical performance between the ALZpath and Fujirebio assays, which could have implications for clinical laboratories when selecting assays and interpreting results. The two assays differ in the methodologies used to detect these low-abundance plasma proteins, as well as in their use of unique proprietary p-tau217 antibodies. The broader measurement range of the ALZpath assay may be attributed to the increased sensitivity of the SIMOA detection method. In contrast, the narrower measurement range of the Fujirebio assay results in a narrower spread in the non-AD cohort.

A limitation of our study is the retrospective nature of the design. Another limitation of our study is that it was conducted in a single laboratory using two lots of reagents for each assay over the course of a few months. For clinical assays to be widely adopted across multiple laboratories, standardization efforts will be necessary to ensure consistent long-term performance. Currently, no FDA-approved p-tau217 assays are available, and it is the responsibility of the testing laboratory to maintain internal quality control standards to ensure assay reliability. For broader implementation, FDA approval will be essential.

In conclusion, this study, along with previous research, suggests the use of plasma p-tau217 as a diagnostic tool to distinguish AD pathology. In this head-to-head comparison, both assays demonstrate excellent analytical performance and effectively differentiate AD pathology from non-AD neurodegenerative diseases. Overall, a three-range approach can be used with both assays resulting in an intermediate zone of 15%–30%, with follow-up confirmation for the intermediate zone cases by PET or CSF testing. Further studies in real-world memory clinics using these cutoff points are necessary to fully evaluate the effectiveness of plasma p-tau217 in routine practice.

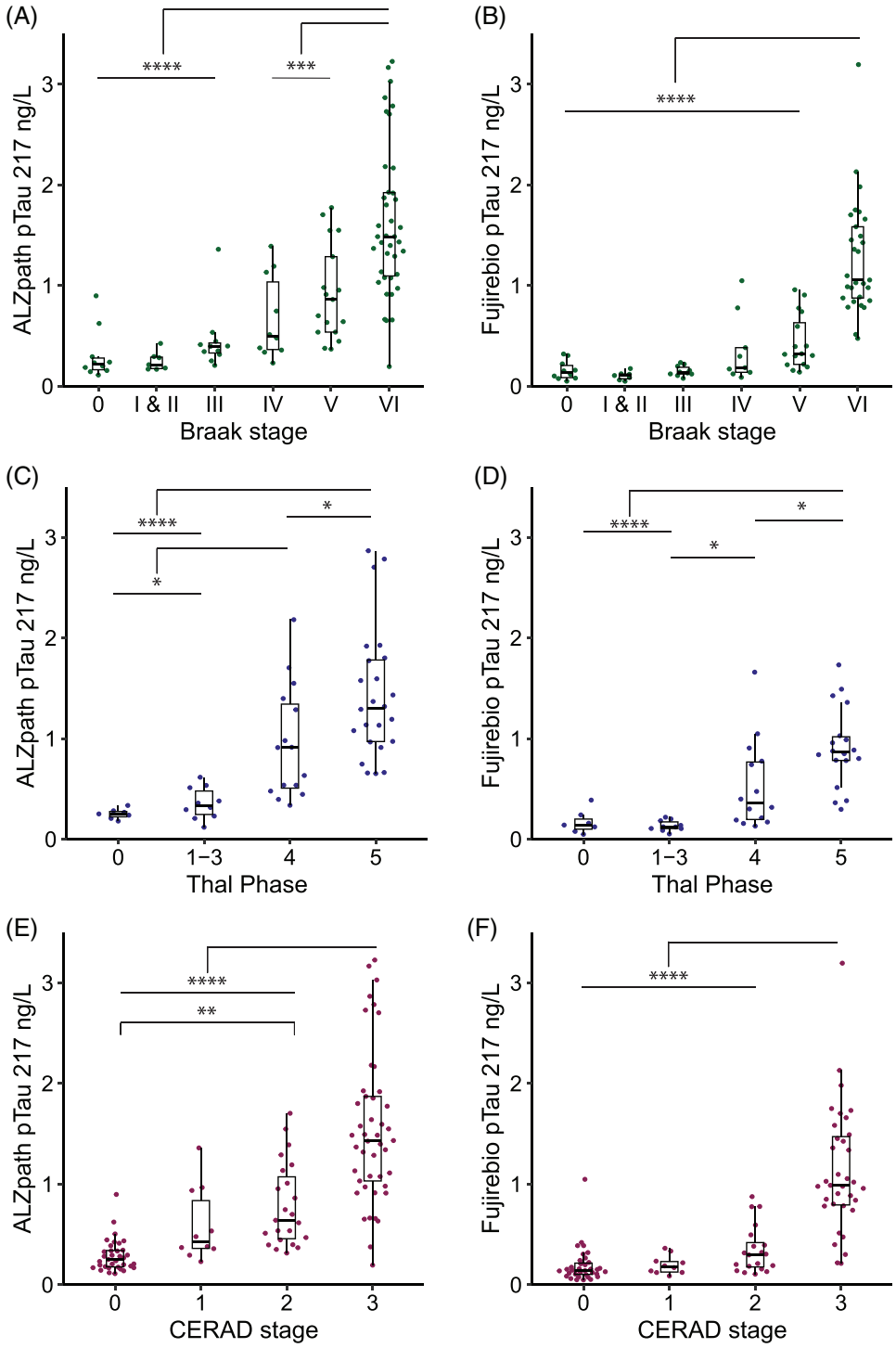

FIGURE 3 Neuropathologic evaluation of tau and amyloid-β scale compared to ALZpath and Fujirebio p-tau217 biomarkers. (A, B) Strong association with NFT burden based on Braak stages for both p-tau217 assays. (A) Visual inspection of the data suggests a biological effect in plasma p-tau217 at Braak stage III with the ALZpath assay and (B) stage IV with the Fujirebio assay. (C, D) Diffuse Aβ plaque burden based on Thal phases. (C) Sequential increased at each Thal phase for ALZpath p-tau217 and (D) stage 4 and 5 for Fujirebio p-tau217. (E, F) Neuritic plaque location and density based on CERAD score. (E) Sequential increase at each CERAD stage observed for ALZpath p-tau217, (F) increase observed at CERAD stage 2 and 3 for Fujirebio p-tau217. Pairwise comparison using Tukey's HSD test; *p-value < 0.05, **p-value < 0.01, ***p-value < 0.001, and ****p-value < 0.0001. CERAD, Consortium to Establish a Registry of Alzheimer's Disease; HSD, honestly significant difference; NFT, neurofibrillary tangle; p-tau, phosphorylated tau.

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CONFLICT OF INTEREST STATEMENT

A.E.M., K.H., D.B., and P.G. are employees of Neurocode USA, Inc. Neurocode was involved in the writing and editorial support of this article. H.F. is a full owner of BC Neuroimmunology (BCNI), and M.E. and A.M. are employees of BCNI. G.R.H. discloses that he has received grants or contracts from CIHR, NIA/NIH, has been a clinical trials investigator supported by Biogen, Cassava, and Lilly, has participated in expert advisory committee supported by Biogen, Eisai, Lilly, and NovoNordisk, and is the current president of C5R (Consortium of Canadian Centres for Clinical Cognitive Research). I.R.M. received grants or contracts from CIHR, Alzheimer's Association US, NIH, Brain Canada, Alzheimer Society of Canada, and Eli Lilly. V.H.-R. is an employee at Vancouver Coastal Health Research Institute. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

Ethical approval was sought from the Research Ethical Board (REB) at the University of British Columbia. Informed consent for the collection of relevant clinical information and the assessment of test results was obtained from the patients or their legal next of kin.

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SUPPORTING INFORMATION

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

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