Title:Comprehensive Clinical and Analytical Validations of Two Novel Plasma pTau217 Immunoassays in a Clinical Diagnostic Laboratory

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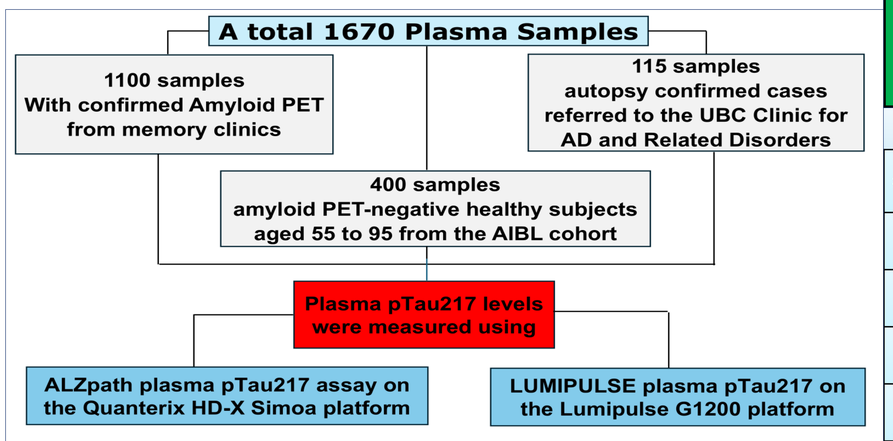
Background

AD is a biological process that begins with the appearance of neuropathological changes when individuals are asymptomatic, and the progression of this neuropathological burden leads to the clinical symptoms observed in AD. Recently, NIA-AA proposed new guidelines for the biological diagnosis of AD (Table 1) [1]. Plasma pTau 217 is a robust biomarker for the diagnosis and monitoring of AD and maps onto either the amyloid beta or AD tauopathy pathway. Several immunoassays have been developed for measuring plasma p-tau217.[2] We assessed the clinical and analytical performance of two novel laboratory-developed pTau217 immunoassays.

Table 1. Categorization of fluid analyte and imaging biomarkers.

Biomarker category	CSF or plasma analytes	Imaging
Core Biomarkers		
Core 1		
A (Aβ proteinopathy)	Aβ 42	Amyloid PET
T$_1$: (phosphorylated and secreted AD tau)	p-tau217, p-tau181, p-tau231	
Core2		
T$_2$ (AD tau proteinopathy)	MTBR-tau243, other phosphorylated tau forms (e.g., p-tau205) non-phosphorylated mid-region tau fragments	Amyloid PET
Biomarkers of non-specific processes 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	αSyn-SAA	

Methods



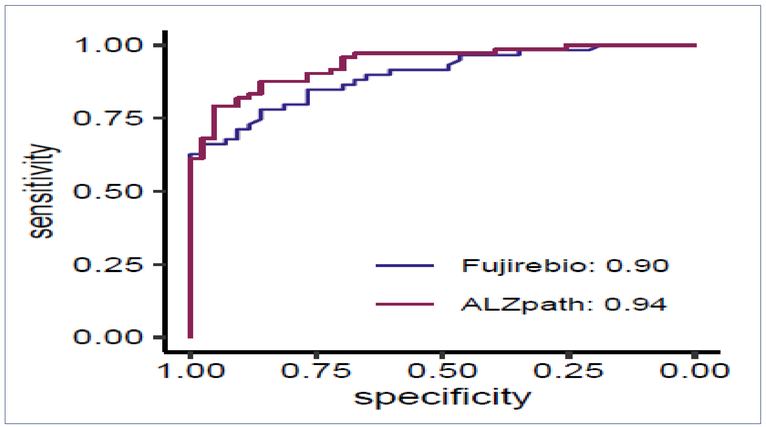
Results

Analytical performance	ALZpath pTau 217	Lumipulse pTau 217
Limit of blank (LoB)	0.0035 ng/L	0.040 ng/L
Limit of detection (LoD)	0.0074 ng/L	0.052 ng/L
Limit of quantification (LoQ)	0.032 ng/L	0.060 ng/L
Clinical reportable range	0.032 – 10.00 ng/L	0.06 – 10.00 ng/L
Intra-laboratory precision	≤ 9.1% above LLoQ	≤ 12.3% above LLoQ
Sample Stability	≤ 7 days at 2 - 8°C ≤ 4 weeks -20°C ≤ 5 freeze/thaw cycles	≤ 7 days at 2 - 8°C ≤ 1 weeks -20°C ≤ 3 freeze/thaw cycles
Interference	No interference detected to the maximum concentration for bilirubin (unconjugated and conjugated), hemoglobin, intralipid, biotin, and heterophilic antibodies	No interference detected to the maximum concentrations for bilirubin (unconjugated and conjugated), hemoglobin, and intralipid. Interference was detected for heterophilic antibodies
Clinical performance	AUC of 0.94 Youden Index of 0.63 ng/L 90.6% NPV – 0.34 ng/L 96.6% PPV – 0.63 ng/L	AUC of 0.90 Youden Index of 0.28 ng/L 90.9% NPV – 0.13 ng/L 93.0% PPV – 0.37 ng/L

ALZpath pTau 217 plasma interlaboratory coefficient of variation (% CV)

Sample ID	p-Tau 217 (mean ± SD)	N	U.S. Intra-lab	Can. Intra-lab	Inter-lab
NC-20	0.25 ± 0.026 ng/L	54	9.1%	11.7%	10.4%
NC-30	0.43 ± 0.044 ng/L	53	7.5%	12.4%	10.4%
MC-40	0.71 ± 0.068 ng/L	44	7.8%	11.5%	9.6%
HC-120	1.94 ± 0.19 ng/L	54	7.0%	12.0%	9.9%

Results



Conclusion

Overall, the analytical performance of the two pTau 217 assays was comparable in two clinical diagnostic laboratories. The reference range curve could be plotted with high certainty using the data from the 400 AIBL samples. The clinical separation between the the healthy controls and those with Amyloid pathology was nearly complete for Alzpath with and AUC of 0.95. The Fujirebio assay had an AUC of 0.90. Similar data was obtained in the two laboratories.

References

1. 1. Jack CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimer's & Dementia*. 2024;20(8):5143-5169. doi:10.1002/alz.13859
2. Mammel AE, Hsiung GYR, Mousavi A, et al. Title: Alzheimer's disease clinical decision points for two plasma p-tau217 laboratory developed tests in neuropathology confirmed samples Abbreviated. doi:10.1101/2024.07.27.24310872

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