Analytical Feasibility of a Composite Plasma Phosphorylated Tau and Aβ Biomarker for Predicting Amyloid PET Positivity

Anthony W. Bannon, PhD; William Z. Potter, MD, PhD; Stephen Zicha, PhD; Leslie M. Shaw, PhD; Jeffrey L. Dage, PhD; Ziad S. Saad, PhD; Iwona Dobler, PhD; David L. Raunig, PhD; Kyle Ferber, PhD; Carrie E. Rubel, PhD; Henrik Zetterberg, MD, PhD; Suzanne E. Schindler, MD, PhD; Michael Baratta, BA, MCAHPM; Emily A. Meyers, PhD; Edwin C. Stage, PhD; Erin G. Rosenbaugh, PhD

The Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium Plasma Aβ Project Team

And Study Collaborators from ADx NeuroSciences/Amsterdam University Medical Centers, Fujirebo Diagnostics, Quanterix, and Roche Diagnostics

BACKGROUND and OBJECTIVES

- The FNIH Biomarkers Consortium Plasma Aβ Project previously published on the performance of six plasma β-amyloid (Aβ) assays to predict amyloid PET positivity (Zicha et al., 2022).
- The results from that work (Table 1) demonstrated that, in general, plasma Aβ assays improved the predictive value over age and *Apolipoprotein E* (*APOE)* genotype alone.
- The current study measured pTau181 in the same Alzheimer's Disease Neuroimaging Initiative (ADNI) plasma sample set using four immunoassays and assessed the ability of plasma pTau181 to predict amyloid PET status alone or in combination with plasma Aβ42/Aβ40 data. In addition, initial data examining the predictive value for tau PET are presented.

METHODS

- The project team consists of representatives from pharmaceutical industry, nonprofit/patient advocacy organizations, and academic institutions. The study was conducted in collaboration with *in vitro* diagnostic companies.
- Four plasma pTau immunoassays were utilized, including: ADx NeuroSciences pTau181 Simoa®, Fujirebo Diagnostics Lumipulse® G pTau 181 Plasma, Quanterix Simoa® pTau 181V2 Advantage, and Roche Diagnostics Elecsys® Phospho-Tau (181P) Plasma. The samples were tested in a blinded manner.
- The sample set consisted of 121 plasma samples from the ADNI cohort. See Table 2 for demographic and clinical characteristics information.
- Diagnostic performance for determining amyloid and tau PET positivity was assessed using Receiver Operating Characteristic (ROC) curve analysis for pTau181 alone or in combination with Aβ42/Aβ40.

Table 1. Summary of plasma Aβ to predict amyloid PET status

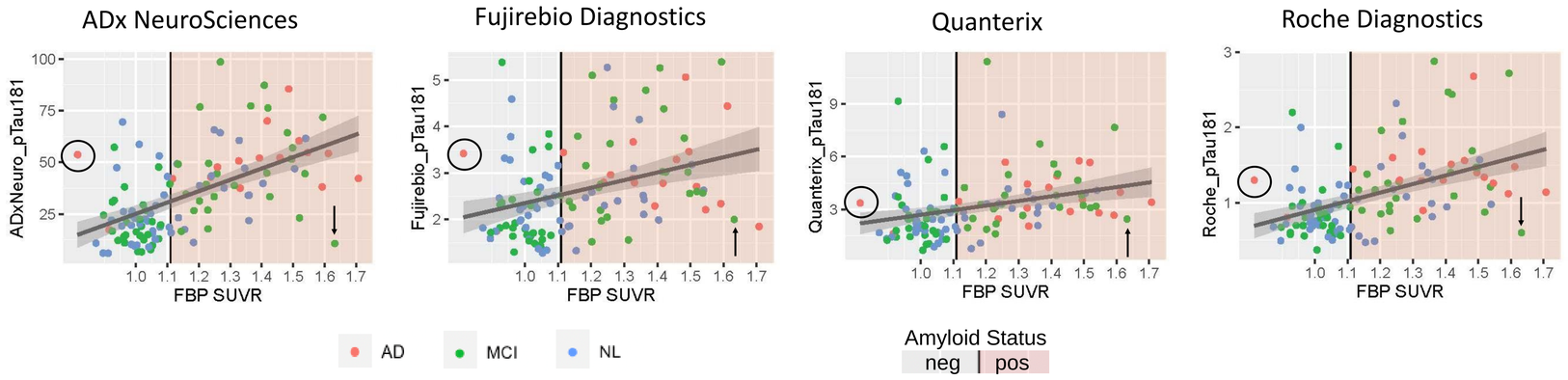
Assay Provider	Assay	Model	AUROC [95% CI]	p-value vs. Ref. Model (one-sided)
		Reference: age, *APOE* genotype	75.0 [66.3, 83.6]	
Washington University at St. Louis	IP-MS	Plasma Aβ42/Aβ40, age, *APOE* genotype	84.2 [77.0, 91.3]	0.0067
		Plasma Aβ42/Aβ40	81.4 [73.6, 89.2]	0.10
Roche Diagnostics	Elecsys cobas e 601	Plasma Aβ42/Aβ40, age, *APOE* genotype	81.1 [73.5, 88.8]	0.024
		Plasma Aβ42/Aβ40	71.0 [61.7, 80.3]	0.73
Shimadzu	IP MALDI-TOF-MS	Plasma Aβ42/Aβ40, age, *APOE* genotype	81.0 [73.4, 88.6]	0.033
		Plasma Aβ42/Aβ40	71.5 [62.5, 80.5]	0.73
University of Gothenburg	IP-MS	Plasma Aβ42/Aβ40, age, *APOE* genotype	78.1 [69.6, 86.7]	0.16
		Plasma Aβ42/Aβ40	64.3 [54.2, 74.3]	0.95
ADx NeuroSciences	Simoa Neuro 4-plex E Kit (Amyblood)	Plasma Aβ42/Aβ40, age, *APOE* genotype	77.0 [68.6, 85.3]	0.21
		Plasma Aβ42/Aβ40	66.1 [56.3, 76.0]	0.91
Quanterix	Simoa Aβ40 and Aβ42 Advantage Kit	Plasma Aβ42/Aβ40, age, *APOE* genotype	76.6 [68.3, 84.9]	0.24
		Plasma Aβ42/Aβ40	64.5 [54.5, 74.5]	0.94

Table 2. Demographic and Clinical Characteristics for ADNI Samples

Characteristics	Amyloid PET Negative (N = 61)	Amyloid PET Positive (N = 60)
Age (years)	77.2 ± 7.3	78.7 ± 6.9
Sex n(% female)	26 (42.6%)	25 (41.7%)
***APOE* genotype**		
2/3	8 (13.1%)	4 (6.7%)
2/4	0	1 (1.7%)
3/3	38 (62.3%)	22 (36.7%)
3/4	14 (23.0%)	22 (36.7%)
4/4	1 (1.6%)	11 (18.3%)
Diagnosis n (%)		
Cognitively Normal	31 (50.8%)	18 (30.0%)
Mild Cognitive Impairment	28 (45.9%)	26 (43.3%)
Dementia	2 (3.3%)	16 (26.7%)
CDR 0/0.5/1/2/3		
Missing CDR data	2	1
0	36	21
0.5	21	21
1	2	16
2	0	1
CDR sum of boxes	0.75 ± 1.38	2.44 ± 2.70
Race n (%)		
White	56 (91.8%)	58 (96.7%)
Black	2 (3.3%)	1 (1.7%)
Other	3 (4.9%)	1 (1.7%)
Years of education	16.6 ± 2.6	16.1 ± 2.9
Florbetapir (FBP) PET SUVR	1.001 ± 0.063	1.347 ± 0.152
MMSE, median (IQR)	29 (28, 30)	27.5 (24, 29.5)
ADAS-Cog 13, median (IQR)	8.00 (5.33, 13.67)	15.84 (8.33, 25.67)

RESULTS

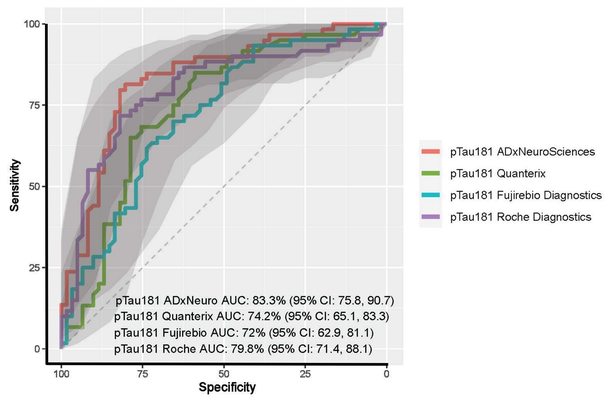
Figure 1. Plasma pTau181 Positively Correlates with Florbetapir SUVR



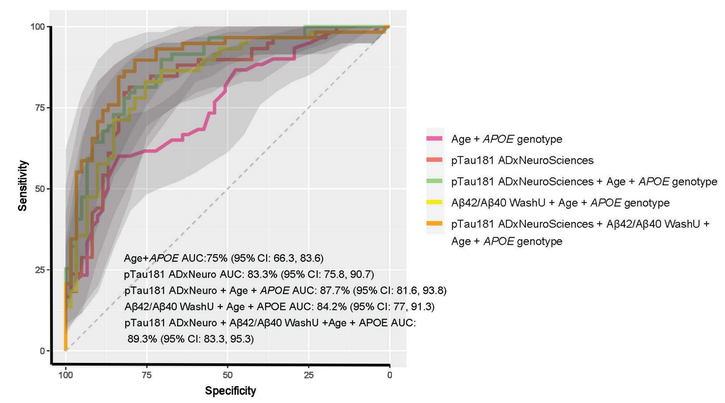
Plasma pTau181 measurements plotted against patient florbetapir (FBP) standardized uptake value ratio (SUVR) values. The vertical line represents the cut-off point for amyloid PET positivity (SUVR ≥ 1.11). The circles and arrows mark plasma pTau181 results that are consistently discordant with FBP SUVR across assays. Abbreviations: AD, Alzheimer's disease; FBP, florbetapir; MCI, mild cognitive impairment; NL, cognitively normal.

Figure 2. ROC Analysis to Discriminate Amyloid PET Positive from Negative Patients

2A



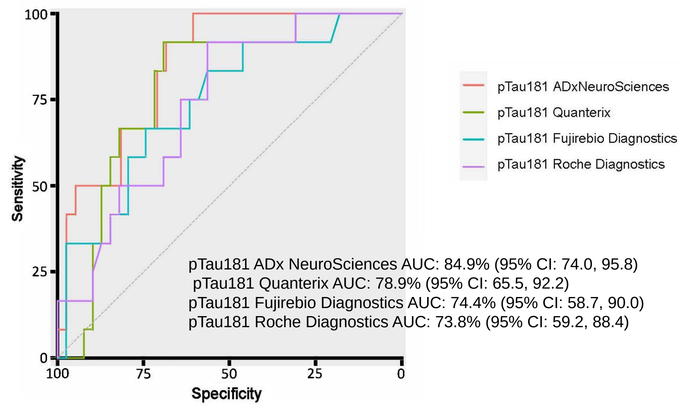
2B



2A. Receiver operating curves for plasma pTau181 alone to predict amyloid PET status.
2B. Adding plasma pTau181 from the ADx NeuroSciences dataset to model using Aβ42/Aβ40 (Washington University at St. Louis dataset, WashU), Age, and *APOE* genotype marginally improved AUC by approximately 4%. However, the resultant AUC with all data variables is comparable to that of model without Aβ42/Aβ40.

Amyloid PET scans using florbetapir (FBP) tracer were within 90 days of blood collection. ADNI participants (n = 121) were categorized as amyloid positive or negative by applying a threshold of FBP SUVR ≥ 1.11 to a cortical summary region normalized by the whole cerebellum reference region (Landau et al., 2013).

Figure 3. ROC Analysis to Discriminate Tau PET Positive from Negative Patients



The four plasma pTau181 assays predicted tau PET status with AUCs ranging from 73.8-84.9%. Tau PET scans using flortaucipir (AV-1451) tracer were within 6 months of blood collection. ADNI participants (n = 66) were categorized as tau positive or negative by applying a threshold of flortaucipir standardized uptake value ratio (SUVR) ≥ 1.25 to a meta-temporal region (Landau et al., AAIC Presentation, July 2022), resulting in 14 tau PET positive and 52 tau PET negative cases.

The sample size for this analysis was small, and the data included were limited to those that had both tau PET and plasma pTau data within 6 months. This may limit the generalizability of the results.

CONCLUSIONS

- Based on this relatively small ADNI cohort, plasma pTau181 measurements predicted amyloid PET status at least comparably to plasma Aβ42/Aβ40 measures with AUCs of 72.0-88.3%.
- The addition of pTau181 to models including Aβ42/Aβ40, age and *APOE* genotype marginally improved the AUC by approximately 4%; however, validation in an independent dataset is needed to determine whether this moderate improvement is idiosyncratic to this sample set.
- Based on subgroup analysis of 66 patients, the four plasma pTau181 assays predicted Tau PET status with AUCs of 73.8-84.9%.
- Future analyses will examine plasma pTau217 and pTau231 measurements.

Scan QR code for the project's previous publication on *Comparative analytical performance of multiple plasma Aβ42 and Aβ40 assays and their ability to predict positron emission tomography amyloid positivity.*

For more detailed information on the study design, methods, and results please contact Erin Rosenbaugh (erosenbaugh@fnih.org).

The study dataset and methodological report are publicly available on the ADNI Laboratory of Neuroimaging (LONI) website.