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

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THE FNIH Biomarkers Consortium Plasma Aβ Project team represents of variables from pharmaceutical industry, nonprofit/patient advocacy organizations, and academic institutions. The study was conducted in collaboration with in vivo diagnostic companies.

Four plasma pTau immunoassays were utilized, including: ADx NeuroSciences pTau181 Simoa® and Fujirebio Diagnostics Lumipulse® G pTau 181 Plasma, Quantexx Simoa® pTau 181V2 Advantage, and Roche Diagnostics Elecsys® Phospho-Tau 181P (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.

### 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. 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 florbetapir (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 florbetapir standardized uptake value ratio (SUVr) ≥ 1.25 to a meta-temporal region (Landau et al., AAN 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 comparable 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 ptau121 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.