Update to the Comparative Analytical Performance of Plasma Aβ Assays and their Relationship to Amyloid PET

Stephen Zicha, PhD, Ziad S. Saad, PhD, Leslie M. Shaw, PhD, Anthony W. Bannon, PhD, Carrie E. Rubel, PhD, Suzanne E. Schindler, MD, PhD, Iwona Dobler, PhD, Lei Du-Cuny, PhD, Sarah F. Giardina, PhD, MBA, Hartmuth C. Kolb, PhD, Emily A. Meyers, PhD, Yulia Mordashova, MS, David L. Raunig, PhD, Erin G. Rosenbaugh, PhD, Christopher J. Weber, PhD, Hang Zhang, PhD, Henrik Zetterberg, MD, PhD, Wesley Horton, MS, and William Z. Potter, MD, PhD
The Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium Plasma Aβ Project Team

Introduction

- Robustly validated plasma β-amyloid (Aβ) assays represent a non-invasive and cost-effective alternative to CSF or neuroimaging for early detection of Alzheimer's disease pathology and screening participants for enrollment into clinical trials.
- The FNIH Biomarkers Consortium Plasma Aβ Project previously published on the performance of six plasma Aβ assays to predict amyloid PET positivity (Zicha et al., 2022).
- Results from the comparative analysis (Table 2) demonstrated that, in general, plasma Aβ assays improved the predictive value over age and Apolipoprotein E (*APOE*) genotype.
- **The project team updated the previous findings by adding the results of a newly developed immunoassay on the automated, scalable Lumipulse platform.**

Methods

- The project team consists of pharmaceutical industry, patient advocacy, governmental, and academic representatives. The study was conducted in collaboration with in vitro diagnostic companies and academic labs.
- The current study utilized the Lumipulse G β-Amyloid assay to analyze the same 121 plasma samples from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort that were previously tested on three immunoassays and three mass spectrometry-based assays. Refer to Table 1 for the demographic and clinical characteristics.
- Diagnostic performance for predicting amyloid PET positivity was assessed using Area Under the Receiver Operating Characteristic (AUROC) curve analysis for Aβ42/40 alone or with age and *APOE* genotype.
- Spearman correlations of plasma Aβ42/40 with amyloid PET (florbetapir, FBP) standardized uptake value ratio (SUVR) were assessed for the best performing assays.

Table 1. Demographic and Clinical Characteristics for ADNI Samples

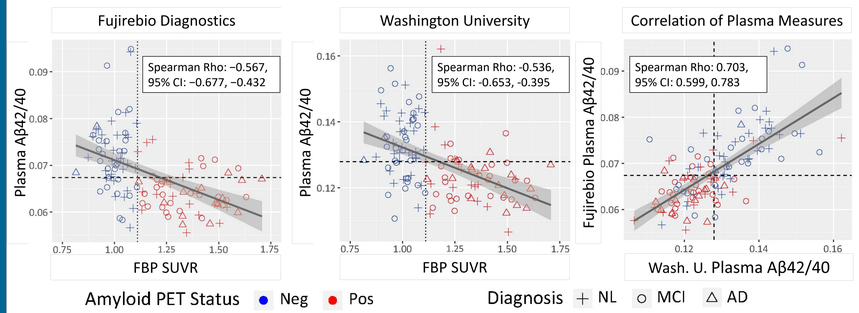
Characteristics	Amyloid PET Negative (N = 61)	Amyloid PET Positive (N = 60)
Age (years)	77.2 ± 7.3	78.7 ± 6.9
Sex n(% female)	26 (42.6%)	25 (41.7%)
***APOE* genotype**		
2/3	8 (13.1%)	4 (6.7%)
2/4	0	1 (1.7%)
3/3	38 (62.3%)	22 (36.7%)
3/4	14 (23.0%)	22 (36.7%)
4/4	1 (1.6%)	11 (18.3%)
Diagnosis n (%)		
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
FlorbetapirET 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

Table 2. ROC Analysis to Discriminate Amyloid PET Positive from Negative Individuals

Assay Provider	Assay	Model	AUROC [95% CI]	p-value vs. Ref. Model (one-sided)
		Reference: age, *APOE* genotype	75.0 [66.3, 83.6]	
Fujirebio Diagnostics	Lumipulse® G β-Amyloid	Plasma Aβ42/Aβ40, age, *APOE* genotype (Full Model)	85.7 [79.1 – 92.4]	0.003
		Plasma Aβ42/Aβ40	82.9 [75.4 , 90.4]	0.073
Washington U. in St. Louis	IP-MS	Full	84.2 [77.0, 91.3]	0.0067
		Plasma Aβ42/Aβ40	81.4 [73.6, 89.2]	0.10
Roche Diagnostics	Elecsys®	Full	81.1 [73.5, 88.8]	0.024
		Plasma Aβ42/Aβ40	71.0 [61.7, 80.3]	0.73
Shimadzu	IP MALDI-TOF-MS	Full	81.0 [73.4, 88.6]	0.033
		Plasma Aβ42/Aβ40	71.5 [62.5, 80.5]	0.73
University of Gothenburg	IP-MS	Full	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)	Full	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	Full	76.6 [68.3, 84.9]	0.24
		Plasma Aβ42/Aβ40	64.5 [54.5, 74.5]	0.94

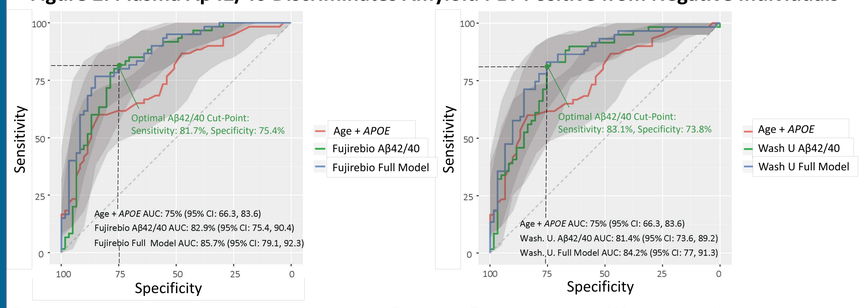
Figure 1. Plasma Aβ42/40 Measures are Correlated Between Assays and with FBP SUVR



Left and middle panels: Plasma Aβ42/40 measures for the Fujirebio Diagnostics and Washington University assays plotted against florbetapir (FBP) standardized uptake value ratio (SUVR) values. The vertical lines represent the cut-point for amyloid PET positivity (SUVR ≥ 1.11). The horizontal lines represent the optimal (Youden) plasma Aβ42/40 cut-point for determining amyloid positivity.

Right panel: Plasma Aβ42/40 measurements for the Washington University plotted against those for the Fujirebio Diagnostics. The dashed lines represent optimal assay plasma Aβ42/40 cut-points.

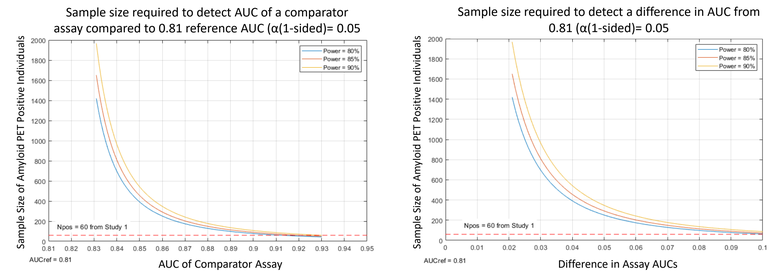
Figure 2. Plasma Aβ42/40 Discriminates Amyloid PET Positive from Negative Individuals



Receiver operating characteristics curves for Fujirebio Diagnostics and Washington University assay plasma Aβ42/40 measures to predict amyloid PET status. The reference model is age and *APOE* genotype. The full model includes age, *APOE* genotype, and plasma Aβ42/40.

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. A Much Larger Cohort is Needed to Differentiate Assay Performance



Sample size estimation using the DeLong variance estimate is shown for the AUROC comparisons of two different Aβ42/40 assays to predict amyloid PET positive subjects. The reference AUC of 0.81 (AUCref) is the AUC for the reference model of the Washington University assay. The parameters for the comparator AUC used the Fujirebio Aβ42/40 assay results for the model parameters. The red dashed reference sample size is the number of amyloid PET positive subjects used in the Study 1 assay comparisons. Approximately 4,000 subjects (2,000 each amyloid PET positive and negative) are needed to differentiate between the Fujirebio Diagnostics and Washington University assays performance at 90% power if AUCs were 0.83 and 0.81, respectively.

Conclusion

- The Fujirebio Diagnostics and Washington University in St. Louis assays perform similarly in predicting amyloid PET status. A much larger sample size than what was analyzed in this study is needed to determine whether one assay has superior performance.
- Results from this comparative analysis together with the continued advancement in plasma assay technology identify a potential use for plasma Aβ42/40 measurement in addressing the amyloid component of the ATN framework.
- The continued advancement and validation of blood assay technology presents a less invasive, more cost-effective, and accessible alternative to neuroimaging or lumbar punctures (for CSF collection) currently used in Alzheimer's diagnosis and monitoring.
- Through extensive validation, the Plasma Aβ Project is establishing blood-based measures as reliable tools in Alzheimer's disease management, opening new possibilities for early intervention and personalized treatment strategies.
- Further evaluation of plasma Aβ42/40 in addition to p-tau, glial fibrillary acidic protein (GFAP), and neurofilament light (NfL) in plasma is planned using longitudinal samples to determine the ability of plasma biomarkers to detect amyloidosis.

Acknowledgments

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Scan QR codes for more information on the Plasma Aβ Project and the project's previous publication

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