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RESEARCH ARTICLE

# Performance of the Lumipulse plasma Aβ42/40 and pTau181 immunoassays in the detection of amyloid pathology

Daniel J. Figdore[1] | Heather J. Wiste[2] | Joshua A. Bornhorst[1] | Randall J. Bateman[3] | Yan Li[3] | Jonathan Graff-Radford[4] | David S. Knopman[4] | Prashanthi Vemuri[5] | Val J. Lowe[5] | Clifford R. Jack Jr[5] | Ronald C. Petersen[4] | Alicia Algeciras-Schimnich[1]

[1]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA

[2]Department of Quantitative Health Sciences, Mayo Clinic, Rochester, Minnesota, USA

[3]Department of Neurology, Washington University School of Medicine, St. Louis, Missouri, USA

[4]Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA

[5]Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA

**Correspondence**
Alicia Algeciras-Schimnich, PhD, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905, USA.
Email: algeciras.alicia@mayo.edu

## Abstract

**INTRODUCTION:** This study evaluated the performance of the Lumipulse plasma beta-amyloid (Aβ) 42/40 and pTau181 compared to other assays to detect an abnormal amyloid-positron emission tomography (PET).

**METHODS:** Plasma samples from cognitively unimpaired ($N$ = 179) and MCI/AD dementia ($N$ = 36) individuals were retrospectively evaluated. Plasma Aβ42/40 and pTau181 were measured using the Lumipulse and Simoa immunoassays. An immunoprecipitation mass spectrometry (IP-MS) assay for plasma Aβ42/40 was also evaluated. Amyloid-PET status was the outcome measure.

**RESULTS:** Lumipulse and IP-MS Aβ42/40 exhibited the highest diagnostic accuracy for detecting an abnormal amyloid-PET (areas under the curve [AUCs] of 0.81 and 0.84, respectively). The Lumipulse and Simoa pTau181 assays exhibited lower performance (AUCs of 0.74 and 0.72, respectively). The Simoa Aβ42/40 assay demonstrated the lowest diagnostic accuracy (AUC 0.57). Combining Aβ42/40 and pTau181 did not significantly improve performance over Aβ42/40 alone for Lumipulse (AUC 0.83) or over pTau181 alone for Simoa (AUC 0.71)

**DISCUSSION:** The Lumipulse Aβ42/40 assay showed similar performance to the IP-MS Aβ42/40 assay for detection of an abnormal amyloid-PET; and both assays performed better than the two p-tau181 immunoassays. The Simoa Aβ42/Aβ40 assay was the least accurate at predicting an abnormal amyloid-PET status.

KEYWORDS
Alzheimer's disease blood biomarkers, amyloid beta, amyloid-PET, Aβ42/Aβ40, plasma pTau, pTau181

## Highlights

- Lumipulse plasma Aβ42/Aβ40 AUC for abnormal amyloid-PET detection was 0.81.

- This performance was comparable to previously reported IP-MS and higher than Simoa.
- Performance of Alzheimer's disease blood biomarkers varies between assays.

## 1 | BACKGROUND

Alzheimer's disease (AD) is the most common cause of dementia.[1] The pathologic changes characteristic of AD are the accumulation of beta-amyloid (A$\beta$) plaques and the presence of intracellular neurofibrillary tangles containing hyperphosphorylated Tau (pTau) species.[2–4] A$\beta$ accumulation is one target for AD therapeutics, and can be measured by amyloid positron emission tomography (PET) imaging.[5–8] Well-established cerebrospinal fluid (CSF) biomarkers such as the ratio of A$\beta$ 1-42 (A$\beta$42) to A$\beta$ 1-40 (A$\beta$40) (A$\beta$42/40), and the ratio of tau phosphorylated at threonine-181 (pTau181) to A$\beta$42 have shown high concordance with amyloid-PET.[9–12] The potentially limited availability of amyloid-PET imaging, invasiveness of CSF collection, and costs associated with both limit the utility of these biomarkers.[13]

Blood-based biomarkers (BBBs) are less invasive and less expensive alternatives to amyloid-PET and AD CSF biomarkers for detecting AD pathology.[13–15] Currently, the Alzheimer's Association's recommendation for BBBs use is limited to two situations: (1) pre-screening of individuals for evidence of AD pathology to assess potential eligibility in therapeutic trials, and (2) use in specialized memory clinics as part of the diagnostic workup in the evaluation of cognitive impairment. In both situations, AD pathology confirmation by AD CSF biomarker testing or PET imaging is recommended.[16]

Although several high sensitivity BBB assays are available, conflicting performance as it relates to diagnostic accuracy has been reported. Various publications have shown that the diagnostic accuracy of plasma A$\beta$42/40 and pTau assay for detection of amyloid pathology can differ significantly between platforms and assay manufacturers.[17,18] Recently, plasma A$\beta$42/40 and pTau assays performed in high throughput and precise instrumentation have become commercially available through Fujirebio Diagnostics, resulting in improved assays' accessibility for research studies and potential clinical use. The aim of our study was to evaluate the performance of the Lumipulse plasma A$\beta$42/40 and pTau181 assays for detection of an abnormal amyloid-PET. We also assessed the performance of these assays against two previously characterized and commonly used assays: a mass spectrometry-based method for plasma A$\beta$42/40[19] and the Quanterix Simoa plasma A$\beta$42/40 and pTau181 immunoassays.[17,18]

## 2 | METHODS

### 2.1 | Participants

All participants were selected through the Mayo Clinic Study of Aging (MCSA) and the Mayo Clinic Alzheimer's Disease Research Center (ADRC) in Rochester, Minnesota. The MCSA is a population-based study in Olmsted County, Minnesota, examining long term cognitive aging in adults to study prevalence, incidence, and risk factors for MCI and dementia with a focus on biomarkers for dementia. MCSA participants are selected as previously described.[20] The Mayo Clinic ADRC is a longitudinal study of participants referred by the Mayo Clinic behavioral neurology practice. All participants underwent extensive cognitive assessment after which a clinical diagnostic classification was determined by an expert consensus panel comprised of those who evaluated each participant.[20] The MCSA and Mayo Clinic ADRC protocols have been approved by the institutional review boards of Mayo Clinic and Olmsted Medical Center. Written informed consent was obtained for all who participated.

The plan for analysis was created after the participants were recruited for inclusion in the MCSA or the Mayo Clinic ADRC and all had received clinical diagnosis, amyloid-PET imaging, pTau181 testing by Simoa assay, A$\beta$42/40 testing by mass spectrometry, and Simoa assay. The plan included testing by the Lumipulse assays and comparing diagnostic accuracy data between available methods. Participants included in this study were taken from an evaluation sample of participants with serial PET and serial plasma between October 2008 and July 2019, spanning a range of amyloid PET standardized uptake value ratios (SUVR). All participants were required to have amyloid PET and plasma measured by Simoa and mass spectrometry methods at the same visit, have a clinical diagnosis of cognitively unimpaired, MCI, or AD dementia, and be 60 years or older; the most recent visit for each individual was used in the analysis. Amyloid-PET was acquired a median (IQR) of 2.2 (1.4, 2.7) months after the blood collection. WashU immunoprecipitation mass spectrometry (IP-MS) testing was performed between August 23, 2021 and November 23, 2021. Simoa testing was performed between September 8, 2021, and March 3, 2022. Lumipulse testing was performed on September 29, 2022, and October 5, 2022. During testing, the laboratories were blinded to the clinical diagnosis, amyloid-PET data, and previous plasma biomarker results.

### 2.2 | Plasma samples

Blood samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes and plasma was separated within 2 h of collection. EDTA-plasma was aliquoted into 1.5 mL polypropylene tubes which were stored frozen at −80°C until testing. Samples were chosen based on the criteria outlined in Section 2.1, and banked sample aliquots were pulled for analysis. Selection based on data availability ensured there was no individuals included with missing data in the analysis.

## 2.3 | Fujirebio Lumipulse assays

The Lumipulse plasma assays were the main focus of this study, as this was the first commercially available set of plasma AD biomarkers on a fully automated continuous loading analyzer with the potential for high throughput clinical testing. Testing was performed on the Fujirebio Lumipulse G1200 automated immunoassay analyzer. EDTA-plasma samples were analyzed directly from the aliquot tubes. The Lumipulse G plasma Aβ42, Aβ40, and pTau181 kits (respective Fujirebio catalog numbers 81301, 81298, and 81288) were used per manufacturer instructions. The reagent kit lot numbers utilized were Aβ42: 2091, Aβ40: 2081, and pTau181: 2071. Specimens were analyzed over 2 days, and manufacturer quality control (QC) material was analyzed before and after testing each day and determined to be within the manufacturer's specifications. Precision based on QC data was < 5% CV for all Lumipulse assays tested.

## 2.4 | Quanterix Simoa assays

Testing was performed at Mayo Clinic in Rochester, Minnesota, by two laboratory technologists trained on the platform by the manufacturer utilizing the Quanterix Simoa HD-X automated immunoassay analyzer. EDTA-plasma samples were analyzed directly from the aliquot tubes. Testing was performed per manufacturer instructions using the Neuro 4-plex E and pTau181 Advantage V2 immunoassay kits (respective Quanterix catalog numbers 103670 and 103714). The reagent kit lot numbers utilized were Neuro 4-plex E kit (Aβ42 and Aβ40): 503085, and pTau181 Advantage V2: 502923. Samples were analyzed in batches with manufacturer provided QC material included in each batch. Precision based on QC data was <7% CV for all Simoa assays tested.

## 2.5 | Aβ42/40 mass spectrometry assay

EDTA-plasma samples were shipped to Washington University (WashU) for Aβ42 and Aβ40 testing by IP-MS developed at WashU. Testing was performed as previously described.[19]

## 2.6 | $^{11}$C Pittsburgh compound B PET imaging

Amyloid-PET imaging was chosen as the reference method due to availability of data in the cohort and its high diagnostic accuracy for detecting AD neuropathology.[6] Amyloid-PET imaging was performed with $^{11}$C Pittsburgh Compound B (PIB),[5] and PET images were analyzed using in-house automated image processing pipeline as described previously.[21] An amyloid-PET standardized uptake value ratio (SUVR) was calculated as the voxel-number weighted average of the median uptake across the following target regions: prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus divided by the median uptake in a cerebellar crus grey matter reference region as previously described.[22] Amyloid-PET was considered abnormal if the SUVR was greater than or equal to 1.52 (Centiloid = 25) to identify intermediate-to-high AD neuropathological changes.[23]

### RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature available in PubMed related to Alzheimer's disease (AD) blood-based biomarkers (BBBs) using the Fujirebio Lumipulse assays as the testing method. While a limited number of publications were identified, none so far had included these assays in a head-to-head comparison with other blood-based biomarker assays.
2. **Interpretation**: In our cohort, the Lumipulse beta-amyloid (Aβ)42/40 assay exhibits an area under the curve (AUC) of 0.81 for detection of an abnormal amyloid-positron emission tomography (PET). Variability in detection of abnormal amyloid-PET was observed among the Aβ42/40 assays included in this study. The diagnostic accuracy of the plasma pTau181 assays was similar for the two platforms evaluated.
3. **Future directions**: Our data support prior findings that diagnostic accuracy performance of AD BBBs can differ significantly between assays and manufacturers. This highlights the need to carefully consider the assay selected for research and clinical purposes, as diagnostic accuracy will be assay dependent and not generalizable.

## 2.7 | Statistical analysis

Spearman's rank correlation coefficient (rho) was calculated to estimate the correlation of each marker with amyloid-PET SUVR. This analysis was repeated for the CU group and MCI/AD group separately to look at differences in correlation between diagnostic groups. Receiver operating characteristic (ROC) analysis was performed to evaluate the sensitivity and specificity of each BBB to identify individuals with an abnormal amyloid-PET. The ROC curve was plotted as sensitivity against 1-specificity and the area under the curve (AUC) was calculated as a measure of performance. Differences in AUC for the individual BBBs were tested using the Delong method. ROC cut points were defined based on the Youden index, which maximizes sensitivity and specificity. Logistic regression models were used to estimate the AUC when using a combination of Aβ42/40 and pTau181. Improvement in AUC from the combination of both BBBs compared to individual BBBs was tested using a jackknife approach.

Agreement between the normal/abnormal BBB status and normal/abnormal amyloid-PET status was expressed as overall percent agreement (OPA), positive percent agreement (PPA), and negative

percent agreement (NPA). OPA was defined as the sum of the number of individuals classified as abnormal by both the BBB and amyloid-PET and the number of individuals classified as normal by both the BBB and amyloid PET, divided by the entire cohort size. PPA was defined as the percent of individuals with abnormal amyloid PET who were classified as abnormal by the BBB. NPA was defined as the percent of individuals with normal amyloid PET who were classified as normal by the BBB. Wilson confidence intervals were reported for OPA, PPA, and NPA. Statistical analysis was performed using the R language and environment for statistical computing version 4.2.2 (R Foundation for Statistical Computing) and Analyse-it version 6.15 for Microsoft Excel.

## 3 | RESULTS

### 3.1 | Participant characteristics

Table 1 summarizes the clinical characteristics and biomarker distribution of the participants. Of the 215 participants, 179 were cognitively unimpaired (CU), 27 had mild cognitive impairment (MCI), and 9 had AD dementia based on consensus clinical diagnosis. The majority of the participants in each group were male (56% CU, 74% MCI, and 78% AD), with median ages ranging from 72 (among AD) to 80 (among MCI) years. In the CU group, 58 (32%) were classified as having an abnormal amyloid-PET, while 17 (63%) in the MCI and 9 (100%) in the AD group had an abnormal amyloid-PET.

### 3.2 | Plasma Aβ42/40 and pTau181 correlation with amyloid-PET

Figure 1 shows the BBBs concentrations plotted against amyloid-PET SUVR, and Table 2 summarizes their respective Spearman's correlation coefficients between diagnostic groups. The Lumipulse Aβ42/40 immunoassay and the Aβ42/40 IP-MS assay showed the strongest correlation with amyloid-PET SUVR with the IP-MS method showing only slightly stronger negative correlation (*rho* values of −0.55 and −0.59, respectively; both $p < 0.001$). The Simoa Aβ42/40 immunoassay exhibited a weaker negative correlation with amyloid-PET (*rho* = −0.17; $p = 0.015$). Lumipulse and Simoa pTau181 immunoassays both had similar positive correlations with amyloid-PET (*rho* values of 0.34 and 0.36, respectively; both $p < 0.001$).

### 3.3 | Plasma Aβ42/40 and pTau181 diagnostic performance

Figure 2 shows ROC curves for detection of an abnormal amyloid-PET. The Lumipulse and IP-MS Aβ42/40 methods were not significantly different with AUCs of 0.81 (95% confidence interval [CI]: 0.75 to 0.86) and 0.84 (95% CI: 0.79 to 0.90), respectively ($p = 0.28$), while Simoa had a significantly lower AUC of 0.57 (95% CI: 0.49 to 0.65, $p < 0.001$). Lumipulse and Simoa pTau181 assays performed similarly to each other with AUCs of 0.74 (95% CI: 0.67 to 0.80) and 0.72 (95% CI: 0.65 to 0.79), respectively ($p = 0.54$). The Lumipulse Aβ42/40 AUC was higher than the Lumipulse pTau181, but not significantly (0.81 vs. 0.74, $p = 0.10$). Modeling the combination of Lumipulse pTau181 with Aβ42/40 did not significantly improve performance compared to the Lumipulse Aβ42/40 alone (AUC of 0.83 [95% CI: 0.78 to 0.89] vs. 0.81, $p = 0.16$). Modeling the combination of Quanterix pTau181 with Aβ42/40 did not improve performance compared to Quanterix pTau181 alone with both having an AUC of 0.71 (95% CI: 0.64 to 0.78).

The BBB cutoffs based on Youden's index cut-points are shown in Table 3, along with the PPA, NPA, and OPA compared to amyloid-PET status. The IP-MS Aβ42/40 showed the highest OPA of the three Aβ42/40 assays evaluated at 79%. Followed by the Lumipulse Aβ42/40 with a OPA of 75%. The Simoa Aβ42/40 demonstrated the lowest PPA, NPA, and OPA at 62%, 55%, and 58%, respectively. The Lumipulse and Simoa pTau181 assays had similar OPA of 68% and 69%, respectively, with a higher PPA than NPA.

## 4 | DISCUSSION

In this study using a cohort that included participants that have undergone amyloid-PET imaging for detection of amyloid pathology, the AUC of the Lumipulse Aβ42/40 immunoassay was 0.81 versus 0.84 for the IP-MS assay. Although the Aβ42/40 IP-MS showed slightly higher AUC, the overlap observed between the AUC 95% CI would suggest that the diagnostic accuracy of these assay is comparable. Previous studies have reported that some plasma Aβ42/40 IP-MS based methods perform better than most immunoassays.[18] Aβ42/40 measured using IP-MS has previously shown high accuracy in detecting amyloid pathology, either compared to amyloid-PET or CSF Aβ42/40, with AUCs ranging from 0.82 to 0.97 depending on the study cohort. This is, to our knowledge, the first report of an Aβ42/40 immunoassay with comparable diagnostic performance to IP-MS methods for Aβ42/40.

We found that the AUC of the Lumipulse Aβ42/40 was higher in this cohort than what was reported for other immunoassays, with AUCs ranging from 0.78 to 0.69.[18] A recent report on the Lumipulse Aβ42/40 immunoassay reported an AUC of 0.86 when using abnormal/normal CSF biomarker results as the outcome measure.[24] In agreement with prior reports, the accuracy for detecting amyloid pathology for the Simoa assay was the lowest in our study cohort (AUC of 0.57). Previous studies have reported AUCs for the Simoa assay ranging from 0.62 to 0.78; with a weighted average AUC of 0.69 across 10 cohorts.[25]

Several immunoassay and MS-based methods have been developed for determination of different pTau species in plasma and used across different studies; however, many of the evaluated blood pTau181 assays are not widely accessible for clinical use in the United States. Like some plasma Aβ42/40 assays, variable performance has been reported for pTau181 immunoassays likely due to the differences in study design and cohort characteristics.[17,26] However, our study did not show a significant difference in the AUCs between the Lumipulse and Simoa pTau181 assays in this cohort. Our findings are in line with Janelidze et al., who reported a Lumipulse pTau181 plasma AUC of

**TABLE 1** Participant demographic characteristics.

| Parameter | CU (*N* = 179) | MCI (*N* = 27) | AD dementia (*N* = 9) | Total (*N* = 215) |
|---|---|---|---|---|
| Age, years | | | | |
| Median (Q1, Q3) | 77 (74, 81) | 80 (72, 85) | 72 (69, 80) | 77 (73, 82) |
| Range | 61–94 | 62–98 | 61–90 | 61–98 |
| Sex | | | | |
| Female | 79 (44%) | 7 (26%) | 2 (22%) | 88 (41%) |
| Male | 100 (56%) | 20 (74%) | 7 (78%) | 127 (59%) |
| APOE ε4 genotype | | | | |
| Non-carrier | 130 (73%) | 19 (70%) | 1 (11%) | 150 (70%) |
| Carrier | 49 (27%) | 8 (30%) | 8 (89%) | 65 (30%) |
| Short test of mental status | | | | |
| Number missing | 1 | 0 | 1 | 2 |
| Median (Q1, Q3) | 35 (33, 37) | 31 (29, 34) | 27 (24, 29) | 35 (33, 36) |
| Range | 24–38 | 27–36 | 16–30 | 16–38 |
| Simoa Aβ42/40 | | | | |
| Median (Q1, Q3) | 0.055 (0.049, 0.063) | 0.059 (0.048, 0.067) | 0.046 (0.040, 0.053) | 0.056 (0.048, 0.063) |
| Range | 0.020–0.155 | 0.013–0.075 | 0.039–0.074 | 0.013–0.155 |
| Lumipulse Aβ42/40 | | | | |
| Median (Q1, Q3) | 0.079 (0.073, 0.088) | 0.076 (0.072, 0.086) | 0.069 (0.065, 0.070) | 0.078 (0.072, 0.088) |
| Range | 0.010–0.279 | 0.047–0.110 | 0.051–0.076 | 0.010–0.279 |
| IP-MS Aβ42/40 | | | | |
| Median (Q1, Q3) | 0.120 (0.112, 0.127) | 0.115 (0.111, 0.121) | 0.112 (0.110, 0.117) | 0.119 (0.111, 0.126) |
| Range | 0.099–0.146 | 0.086–0.134 | 0.107–0.120 | 0.086–0.146 |
| Simoa pTau181 (pg/mL) | | | | |
| Median (Q1, Q3) | 1.87 (1.48, 2.54) | 2.67 (2.04, 3.80) | 2.90 (2.36, 3.47) | 1.99 (1.51, 2.73) |
| Range | 0.66–6.73 | 1.06–8.83 | 2.24–5.70 | 0.66–8.83 |
| Lumipulse pTau181 (pg/mL) | | | | |
| Median (Q1, Q3) | 2.40 (1.88, 3.04) | 3.10 (2.42, 4.08) | 3.35 (3.07, 3.67) | 2.50 (1.97, 3.26) |
| Range | 0.75–6.71 | 1.09–8.58 | 2.12–4.90 | 0.75–8.58 |
| Amyloid PET, SUVR | | | | |
| Median (Q1, Q3) | 1.43 (1.35, 1.60) | 1.78 (1.40, 2.35) | 2.42 (2.31, 2.84) | 1.46 (1.35, 1.73) |
| Range | 1.19–3.30 | 1.22–2.66 | 1.58–3.04 | 1.19–3.30 |
| Amyloid PET, Centiloid | | | | |
| Median (Q1, Q3) | 17 (10, 32) | 48 (14, 98) | 105 (95, 142) | 19 (10, 44) |
| Range | −4–183 | −2–126 | 31–160 | −4–183 |
| Amyloid PET ≥ 1.52 SUVR (25 Centiloid) | | | | |
| Normal | 121 (68%) | 10 (37%) | 0 (0%) | 131 (61%) |
| Abnormal | 58 (32%) | 17 (63%) | 9 (100%) | 84 (39%) |

Abbreviations: Aβ, beta-amyloid; AD, Alzheimer's disease; CU, cognitively unimpaired; IP-MS, immunoprecipitation mass spectrometry; MCI, mild cognitive impairment; PET, positron emission tomography; SUVR, standardized uptake value ratio.

0.69 for detection of amyloid pathology using CSF Aβ42/40 as a comparator in a cohort of individuals with MCI.[18] Wilson et al. reported a plasma AUC of 0.96 to distinguish cognitively unimpaired amyloid negative individuals from patients with AD,[27] while Arranz et al. reported a plasma AUC of 0.91 to distinguish individuals exhibiting both amyloid and tau pathology from amyloid and tau negative individuals compared to CSF biomarkers.[24]

Several factors are taken into consideration when choosing an assay platform to implement in the clinical laboratory with diagnostic accuracy being one of them. Additional factors include assay robustness,

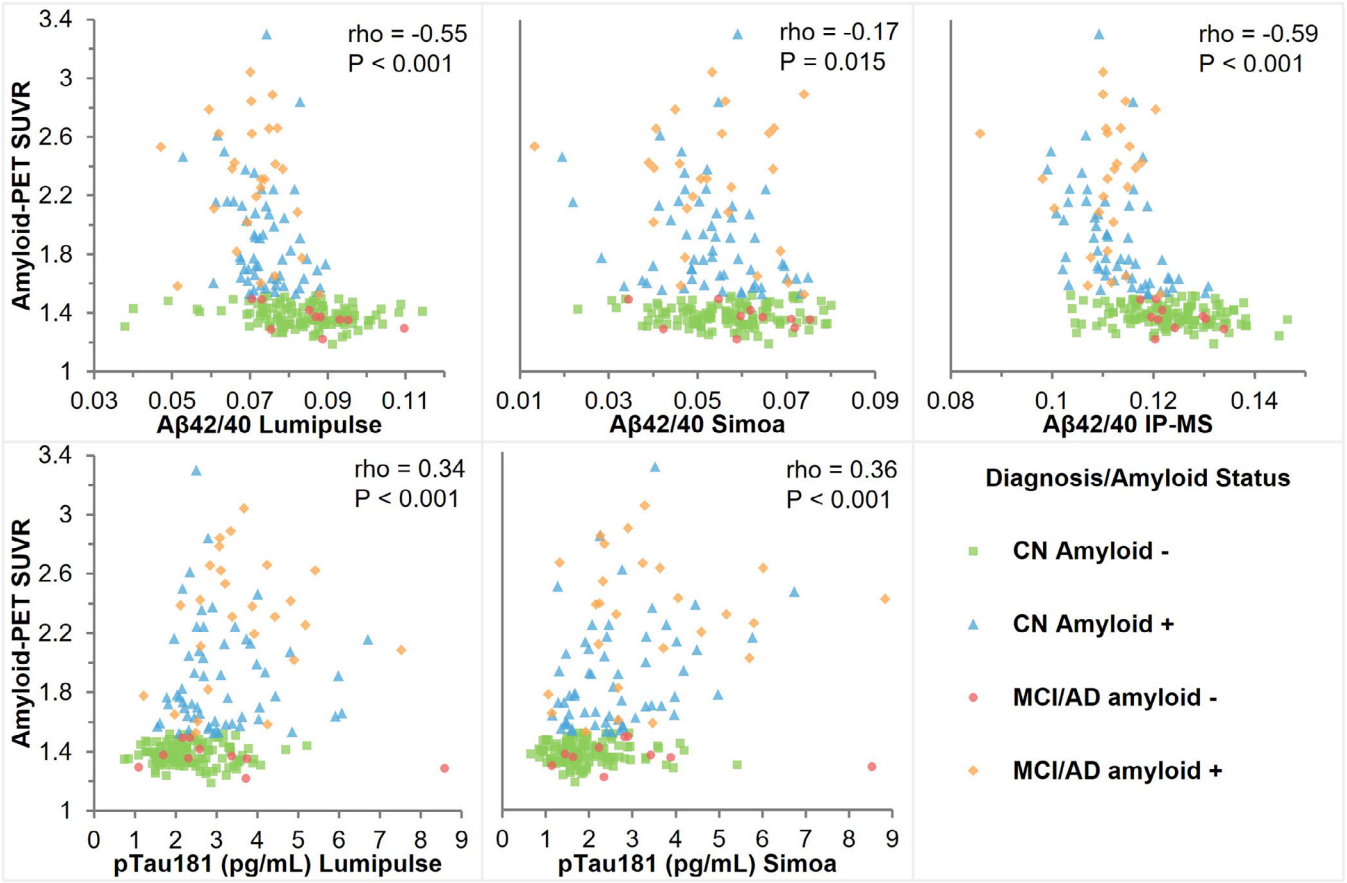


**FIGURE 1** Scatterplots showing the correlation of blood-based biomarker concentrations with amyloid-PET SUVR. Four outlying data points were removed from the Aβ42/40 plots to better visualize correlation on a more legible scale. See Figure S1 for plots of all Aβ42/40 points without these outliers excluded. Aβ, beta-amyloid; PET, positron emission tomography; SUVR, standardized uptake value ratio.

**TABLE 2** Spearman's correlation with amyloid-PET SUVR.

| Assay | All data (*N* = 215) | CU group (*N* = 179) | MCI/AD group (*N* = 36) |
|---|---|---|---|
| Aβ42/40 ratio | | | |
| Fujirebio Lumipulse | −0.55 | −0.48 | −0.56 |
| Quanterix Simoa | −0.17 | −0.14 | −0.25 |
| WashU IP-MS | −0.59 | −0.53 | −0.54 |
| pTau181 (pg/mL) | | | |
| Fujirebio Lumipulse | 0.34 | 0.29 | 0.24 |
| Quanterix Simoa | 0.36 | 0.31 | 0.15 |

Abbreviations: Aβ, beta-amyloid; AD, Alzheimer's disease; CU, cognitively unimpaired; IP-MS, immunoprecipitation mass spectrometry.; MCI, mild cognitive impairment; PET, positron emission tomography; SUVR, standardized uptake value ratio.

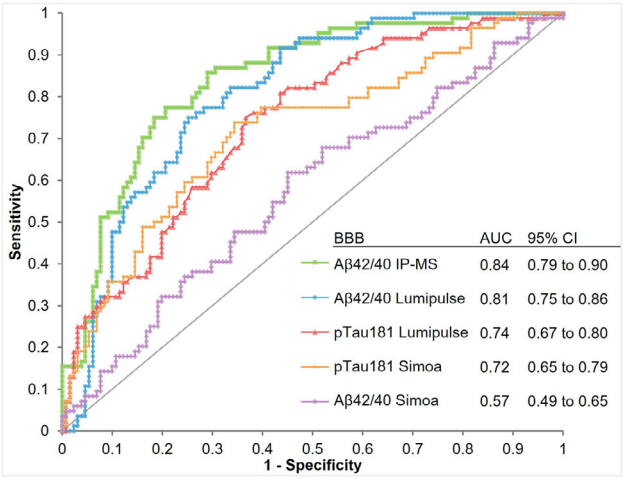


**FIGURE 2** ROC AUC for detection of abnormal amyloid-PET. AUC, area under the curve; PET, positron emission tomography; ROC, receiver operating characteristic.

reagent lot to lot consistency, test complexity, turnaround time (TAT) and cost. From the evaluated assays, IPMS methods tend to have higher equipment costs and higher complexity requiring highly trained technologists, more hands-on time, and have longer TAT. Although IPMS methods have generally shown higher diagnostic accuracy for the analytes than immunoassay, it was only modestly higher in this cohort when compared to the Lumipulse Aβ42/40 assay. High throughput immunoassay platforms are widely used in the clinical laboratory setting. They tend to have higher throughput, easier sample processing, and faster TAT; while maintaining high precision of measurements, making them more amenable to routine clinical use.

**TABLE 3** Youden index cutoffs for blood-based biomarkers and agreement with amyloid-PET.

| Assay | Cutoff | PPA (95% CI) | NPA (95% CI) | OPA (95% CI) |
|---|---|---|---|---|
| Aβ42/40 ratio | | | | |
| Fujirebio Lumipulse | 0.077 | 75% (65%–83%) | 75% (67%–81%) | 75% (69%–80%) |
| Quanterix Simoa | 0.056 | 62% (51%–72%) | 55% (46%–63%) | 58% (51%–64%) |
| WashU IP-MS | 0.117 | 77% (67%–85%) | 79% (72%–85%) | 79% (73%–84%) |
| pTau181 (pg/mL) | | | | |
| Fujirebio Lumipulse | 2.46 | 75% (65%–83%) | 63% (55%–71%) | 68% (61%–74%) |
| Quanterix Simoa | 1.99 | 74% (64%–82%) | 66% (57%–73%) | 69% (62%–75%) |

Abbreviations: Aβ, beta-amyloid; CI, confidence interval; IP-MS, immunoprecipitation mass spectrometry; NPA, negative percent agreement; OPA, overall percent agreement; PET, positron emission tomography; PPA, positive percent agreement.

While our study focused on some of the first commercially available assays (plasma Aβ42/40 or pTau181), recently, plasma pTau217 is emerging as a superior biomarker to plasma Aβ42/40 or pTau181 for detection of amyloid pathology.[28–30] As these biomarkers or combinations of biomarkers become commercially available, the assay robustness and diagnostic accuracy needs to be considered in order to provide assays with the most accurate detection of amyloid pathology and AD diagnosis.

Strengths of this study are the inclusion of clinically characterized participants selected either from a specialized neurology practice or a community-based cohort where patients are randomly selected from the population census, and the use of amyloid-PET as the comparator to BBB assays. A limitation of this study is the relatively small number of MCI and AD patients included. Also, participants of this community-based cohort were predominantly white. Prior studies examining performance of BBBs in racial and ethnic diverse groups have been conflicting[31–34] and more data are needed to determine if the diagnostic performance observed in this study is applicable to more diverse populations. Finally, we used amyloid-PET as the outcome measure; therefore, studies examining performance of BBBs using CSF biomarkers to characterize amyloid pathology may not be directly comparable as CSF markers can also have varying performance for detecting an abnormal amyloid-PET.[35]

In conclusion, we found that, from the Lumipulse plasma assays, the Aβ42/40 has higher diagnostic accuracy than pTau181 for detection of an abnormal amyloid-PET. The AUC of the Lumipulse Aβ42/40 assay was not significantly different than the IP-MS Aβ42/40 assay evaluated in this study. However, the observed differences with the Simoa Aβ42/40 assay confirms prior findings of variability in diagnostic accuracy amongst assays. This highlights the need to carefully consider the assay selected for research and clinical purposes, as diagnostic accuracy will be assay dependent and not generalizable. Finally, the differences in diagnostic accuracy between assays for the same analyte warrant that detailed information on the assay being used in a study or by a clinical laboratory is provided to aid in interpretation of the results.

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## CONFLICT OF INTEREST STATEMENT

Alicia Algeciras-Schimnich has participated in advisory boards for Roche Diagnostics, Fujirebio Diagnostics and Siemens Healthineers. Daniel J. Figdore reports no disclosures. Heather J. Wiste reports no disclosures. Joshua A. Bornhorst has participated on an advisory board for Sunbird Bio and received an honorarium from Roche Diagnostics. Randall J. Bateman has received research funding from Avid Radiopharmaceuticals, Janssen, Roche/Genentech, Eli Lilly, Eisai, Biogen, AbbVie, Bristol Myers Squibb, and Novartis. Washington University and Randall J. Bateman have equity ownership interest in C2N Diagnostics and receive income based on technology (stable isotope labeling kinetics, blood plasma assay, and methods of diagnosing AD with phosphorylation changes) licensed by Washington University to C2N Diagnostics. Randall J. Bateman receives income from C2N Diagnostics for serving on the scientific advisory board. Randall J. Bateman serves on the Roche Gantenerumab Steering Committee as an unpaid member. Yan Li reports no disclosures. Jonathan Graff-Radford receives funding from the NIH. He is an investigator in clinical trials sponsored by Biogen, Eisai and the University of Southern California. David S. Knopman serves on a Data Safety Monitoring Board for the Dominantly Inherited Alzheimer Network Treatment Unit study. He served on a Data Safety monitoring Board for a tau therapeutic for Biogen (until 2021) but received no personal compensation. He is an investigator in clinical trials sponsored by Biogen, Lilly Pharmaceuticals and the University of Southern California. He has served as a consultant for Roche, Samus Therapeutics, Magellan Health, Biovie and Alzeca Biosciences but receives no personal compensation. He attended an Eisai advisory board meeting for lecanemab on December 2, 2022, but received no compensation. He receives funding from the NIH. Prashanthi Vemuri receives funding from the NIH. Val J. Lowe consults for Bayer Schering Pharma, Piramal Life Sciences, Eisai, Inc., AVID

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## CONSENT STATEMENT

All human subjects provided informed consent.

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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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