

Multi-Biomarker Plasma Panels Improve Amyloid-β Prediction and Reduce Intermediate Zones in Preclinical and Clinical Alzheimer’s Disease

P-0402

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The incorporation of age, sex, APOE ε4 status, and additional biomarkers resulted in only small, non-significant improvements in AUC compared with the pTau217/Aβ ratio alone. However, the multivariable models substantially reduced the proportion of individuals classified within the intermediate zone.

INTRODUCTION	RESULTS	RESULTS	RESULTS	CONCLUSIONS
Blood-based biomarkers show high accuracy for predicting amyloid-β (Aβ) positivity in Alzheimer's disease (AD). Key clinical applications include identifying individuals for prevention trials and screening candidates for disease-modifying therapies. This study compared the performance of individual biomarkers and multi-biomarker panels for predicting Aβ positivity across both settings.	In the PCADC, both the p-tau217/Aβ42 ratio and the multi-biomarker panels (Simoa and Lumipulse) demonstrated significantly higher AUC values than p-tau217 alone; however, the multivariate panels did not significantly outperform the p-tau217/Aβ42 ratio (p > 0.05). In the ITTC, the Quanterix p-tau217/Aβ42 ratio did not improve AUC compared with p-tau217 alone (p = 0.55), whereas the multi-biomarker panel showed superior performance (p = 0.01). In contrast, both the Lumipulse p-tau217/Aβ42 ratio and the multi-biomarker panel outperformed p-tau217 alone (p < 0.012).	In the PCADC, intermediate zones were smaller for multi-biomarker panels compared with single biomarkers and ratios, with Quanterix intermediate zones of 26%, 10%, and 2% for p-tau217, p-tau217/Aβ42, and the multi-biomarker panel, respectively, and Lumipulse intermediate zones of 29%, 15%, and 15% respectively.	In the ITTC, intermediate zones were consistently lowest and accuracy highest for multi-biomarker panels, with Quanterix having intermediate zones of 12%, 13%, and 3%, and Lumipulse having intermediate zones of 23%, 13%, and 0.5% for p-tau217, p-tau217/Aβ42, and multi-biomarker panels, respectively.	The pTau217/Aβ ratio demonstrated excellent performance as a standalone predictor of amyloid positivity. However, incorporation of age, sex, APOE ε4 status, and complementary plasma biomarkers substantially reduced intermediate-zone classifications while maintaining high diagnostic accuracy. Multi-biomarker approaches therefore have the potential to improve clinical decision-making, reduce reliance on confirmatory PET and CSF testing, and facilitate scalable blood-based screening strategies in both research and clinical settings.
METHODS				
Participants from the Australian Imaging, Biomarkers and Lifestyle study were grouped into two cohorts: a preclinical AD cohort (PCADC; N = 123) and an intention-to-treat cohort (ITTC) (mild cognitive impairment or Alzheimer's disease; N = 200). Receiver operating characteristic analyses evaluated individual or multi-biomarker panel measurements using Lumipulse and Simoa platforms (p-tau217, p-tau181, Aβ42, Aβ40, BD-tau, GFAP, and neurofilament light) for prediction of Aβ-PET positivity. Area under the curve (AUC) values and intermediate zones were compared using DeLong's test and a conservative 95% for sensitivity and specificity cut-offs.				
Figure 1: Box and whisker plot of biomarker values between Aβ-status, cohort and platform. ROC curves per biomarkers to predict Aβ-status across cohort and platform. Figure 2: Dual cut-off distributions across biomarkers and platform within the PCADC. Figure 3: Dual cut-off distributions across biomarkers and platform within the ITTC.				
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