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BIOMARKERS

POSTER PRESENTATION

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BIOMARKERS (NON-NEUROIMAGING)

Plasma biomarkers predict incident cognitive decline up to 29 years prior to disease onset: a memory clinic cohort study of 4,073 participants

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Abstract

Background: Plasma biomarkers have demonstrated excellent performances in detecting AD/ADRD-related brain pathology. However, their relationship with cognitive decline remains unclear. We examined this in a large memory clinic cohort with baseline plasma biomarkers and repeated cognitive assessments over approximately three decades.

Method: Participants at the University of Pittsburgh Alzheimer's Disease Research Center underwent blood collection and Clinical Dementia Rating (CDR) Sum of Boxes-based cognitive assessment cross-sectionally, followed by annual CDR assessments for up to 29 years (3.0 [IQR 1.9-5.9]). Plasma *p*-tau181, *p*-tau217, brain-derived tau (BD-tau), GFAP and NfL, were measured using SIMOA assays. Linear/logistic regression and Fisher's exact were employed for statistical inference.

Result: We included 4,073 participants (59.9% female; 90.2% self-identified non-Hispanic White), aged 71.9 ± 9.8 years, with 2160 being non-demented (CDR≤0.5) at baseline. Cross-sectionally, higher levels of all biomarkers were significantly associated with worse CDR scores. Longitudinally, baseline *p*-tau181 and GFAP levels best predicted cognitive decline at 0-2, 2-5, 5-10, and >10 years. In contrast, *p*-tau217 was superior at predicting whether cognitive decline would happen at all within 2, 5, or 10 years, with AUCs up to 0.810. Participants with above-median *p*-tau217 levels had

the highest odds of cognitive decline (2.57, 4.53, and 10.34 times within 2, 5 and 10 years, respectively). *p*-tau217, and *p*-tau217/BD-tau ratio accounting for CNS-derived *p*-tau217, were most effective in predicting cognitive decline in participants who were cognitively non-demented at baseline. Importantly, cognitively stable individuals had lower levels of all plasma biomarkers vs. progressors, with *p*-tau217 best at separating these groups.

Conclusion: Leveraging a large cohort with extensive longitudinal data, our findings underscore the significant value of blood-based biomarkers in predicting cognitive decline to aid personalized clinical management and ultimately improve patient outcomes.