

The Multi-Dementia Panel provides biological insights and robust diagnostic and prognostic value in Alzheimer's disease

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BACKGROUND

- Efficient **evaluation of therapeutic response** in clinical trials for Alzheimer's disease (AD) requires biomarkers reflecting the **diverse pathological pathways**.^{1,2}
- We previously developed **two CSF biomarker panels** leveraging proximity extension assay (PEA) technology that capture diverse biological processes in AD.³
 - The **AD diagnostic panel** discriminated AD patients from healthy controls (CON) with areas under the receiver operating characteristic curve (AUCs) of 0.94 to 0.99.
 - The **AD differential diagnostic panel** discriminated AD from non-AD dementia patients with AUCs of 0.80 to 0.87.

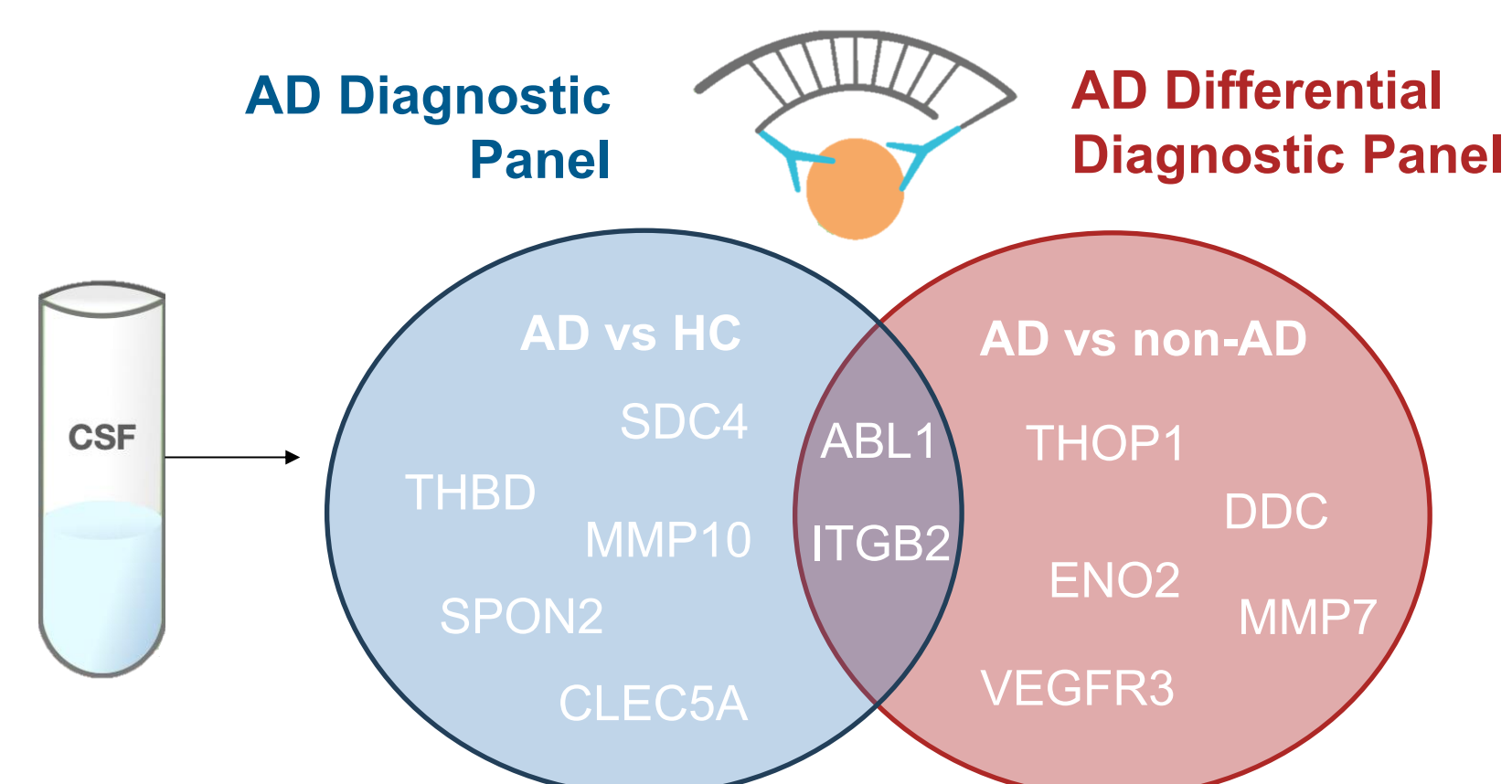
AIM

Validate the **diagnostic robustness** and explore the **prognostic value** of our **AD diagnostic** and **AD differential diagnostic** panels

METHODS

STUDY DESIGN

- The **AD diagnostic** (7 proteins) and **AD differential diagnostic** panels (7 proteins) are custom PEA (Olink) assays.
- Panels were measured in participants from the **University of California San Diego Shiley-Marcos AD Research Centre**



	CON	MCI-AD	AD	FTD	LBD
	n = 109	n = 41	n = 37	n = 16	n = 17
Female, n (%)	66 (61)	14 (34)	19 (51)	9 (56)	3 (18)
Age, Mean (SD)	73 (6)	76 (5)	71 (7)	63 (7)	73 (7)
MMSE, Median [IQR]	30 [1]	28 [3]	23 [6]	23 [7]	27 [6]

- For 10 dementia and 24 MCI-AD patients, **Mini-Mental State Examination (MMSE) follow-up** (mean time interval of 6 years, range 3 to 13 years) was available.

METHODS

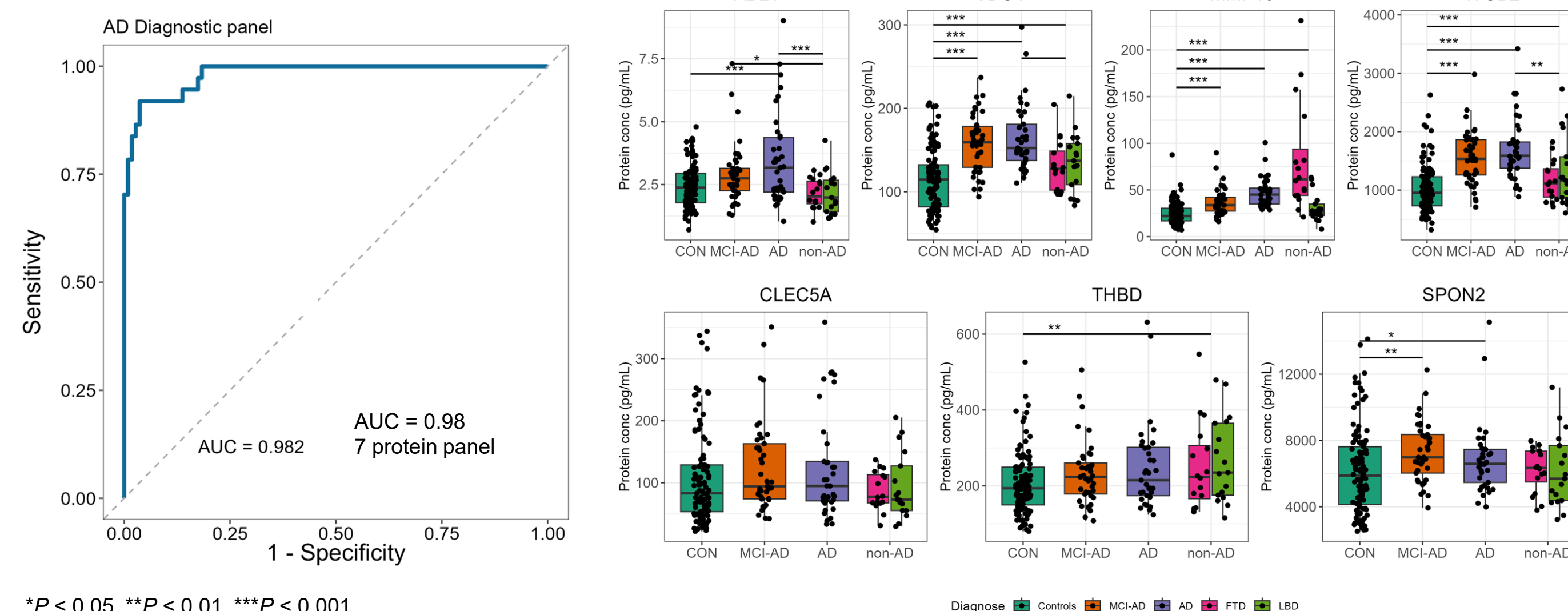
STATISTICAL ANALYSIS

- Diagnostic performance to discriminate AD patients from CONs (**AD diagnostic panel**) and non-AD dementia patients (**AD differential diagnostic panel**) was validated using **receiver operating characteristic (ROC) analysis**.
- Prognostic value was explored by:
 - Primary linear mixed-effects (LME) model:** Derive subject-specific MMSE slopes.
 - Ridge regression:** Predict unbiased subject-specific weighted panel risk scores using MMSE slope (from primary LME model) as outcome and z-scored biomarkers within each panel as predictors through five-fold nested cross validation.
 - Secondary LME models:** Evaluate the predictive effect of CSF panel risk scores (as derived from ridge regression) for MMSE decline (as derived from the primary LME model).

RESULTS

VALIDATION OF DIAGNOSTIC VALUE

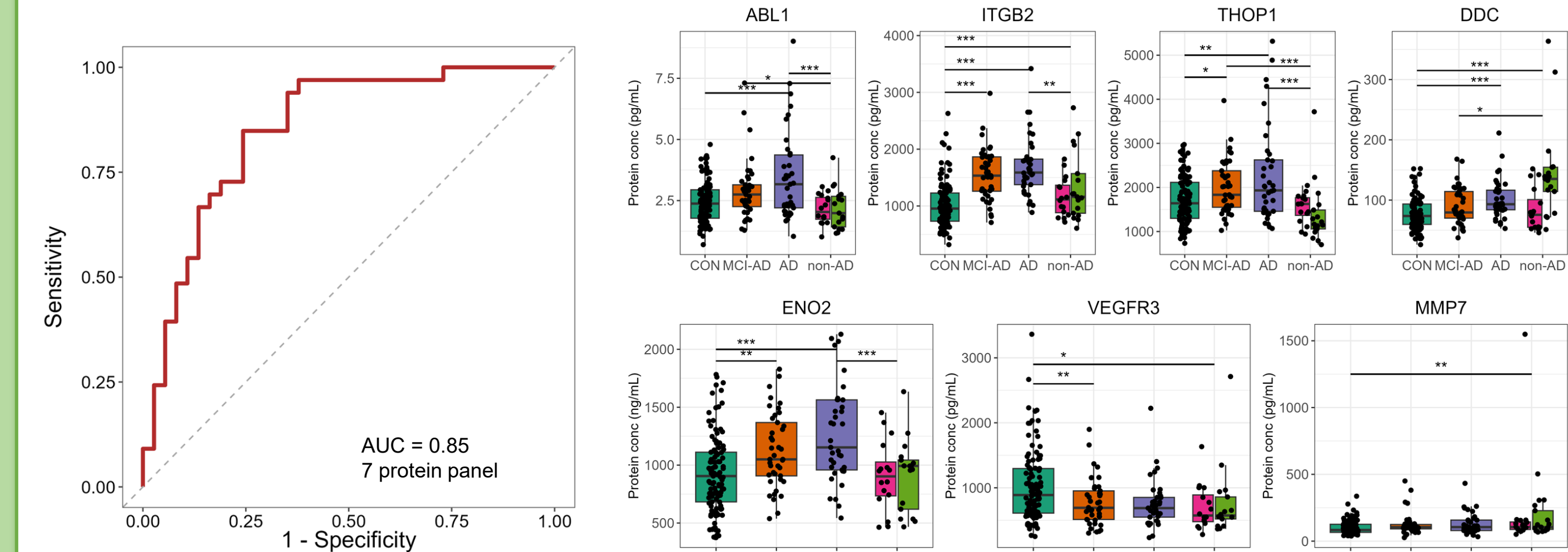
The **AD diagnostic panel** discriminated AD patients from CONs with comparably high accuracy (AUC = 0.98) as the initial study.



*P < 0.05, **P < 0.01, ***P < 0.001

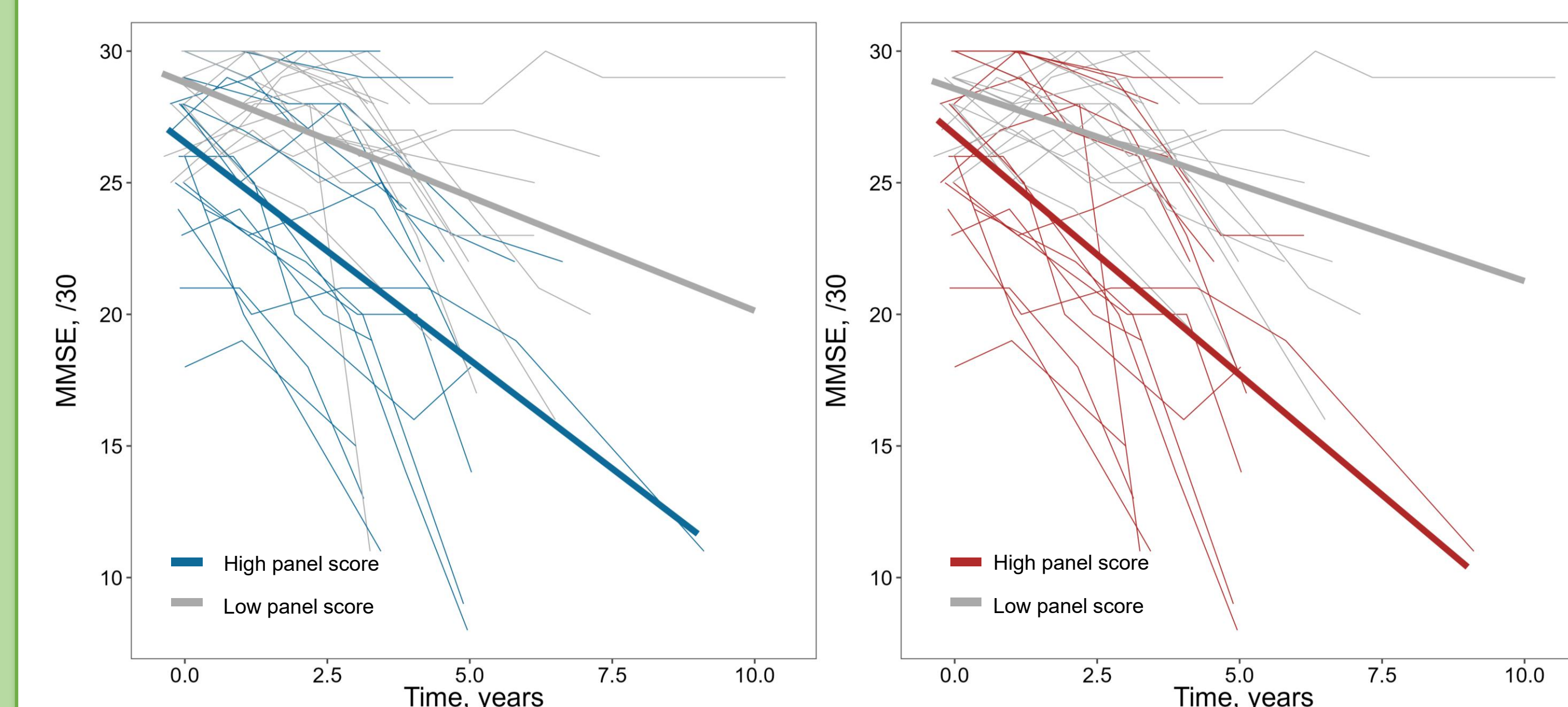
The **AD differential diagnostic panel** also distinguished AD from non-AD patients with comparable accuracy (AUC = 0.85) to the initial study.

RESULTS



EXPLORATION OF PROGNOSTIC VALUE

Within the AD subgroup, the **diagnostic** ($\beta_{\text{time} \times \text{panel score}}$ [95% CI] = 1.01 [0.39 to 1.63], $P = .0025$) and **differential diagnostic** panels ($\beta_{\text{time} \times \text{panel score}}$ [95% CI] = 0.95 [0.37 to 1.54], $P = .0024$) both demonstrated predictive value for MMSE decline.



ABL1 (kinase involved in cytoskeletal remodeling) and ITGB2 (immune function) were among the highest-weighted proteins in both panels, alongside MMP10 (peptidase) and ENO2 (energy metabolism) in respectively diagnostic and differential diagnostic panels.

CONCLUSION

- Our custom CSF PEA biomarker panels capture the biological diversity of AD and provide **robust (differential) diagnostic performance as well as prognostic information**.
- These panels support **patient stratification and tracking of diverse biological responses** in clinical trials.

References:

- Oosthoek M, Vermunt L, de Wilde A, et al. Utilization of fluid-based biomarkers as endpoints in disease-modifying clinical trials for Alzheimer's disease: a systematic review. *Alzheimers Res Ther.* 2024 Apr 27;16(1):93.
- Cummings J, Sharma S, DeAndrea G, Leisgang Osse A, Ortiz A. The roles of biomarkers in Alzheimer's disease clinical trials. *Neurotherapeutics.* 2026 Jan;23(1):e00811.
- Del Campo M, Peeters CFW, Johnson ECB et al. CSF proteome profiling across the Alzheimer's disease spectrum reflects the multifactorial nature of the disease and identifies specific biomarker panels. *Nat Aging.* 2022 Nov;2(11):1040-1053.