

Plasma APOE4 Proteotyping Enables Accurate Carrier Classification And Reveals Molecular Links To Alzheimer's Risk

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Key Message

APOE4 proteotyping captures genotype-level risk and becomes most useful when embedded in a multiplex AD plasma biomarker panel.

Background

- APOE ϵ 4 is the strongest genetic risk factor for late-onset AD and confers dose-dependent amyloid risk.
- APOE status is usually determined by DNA genotyping, but plasma proteotyping can measure APOE4-specific protein signal in the same blood-based workflow as other AD biomarkers
- This makes APOE4 proteotyping attractive for scalable risk assessment and mechanistic biomarker profiling

Methods

- Participants
Multi-cohort (ADRC, ALPS, LATTICE, and HeartSCORE) plasma obtained from 1,658 individuals

- Paired measurements
Plasma NULISAseq CNS panel + TaqMan APOE genotyping

- Carrier classification
ROC/Youden thresholds for carrier status and ϵ 4 copy number

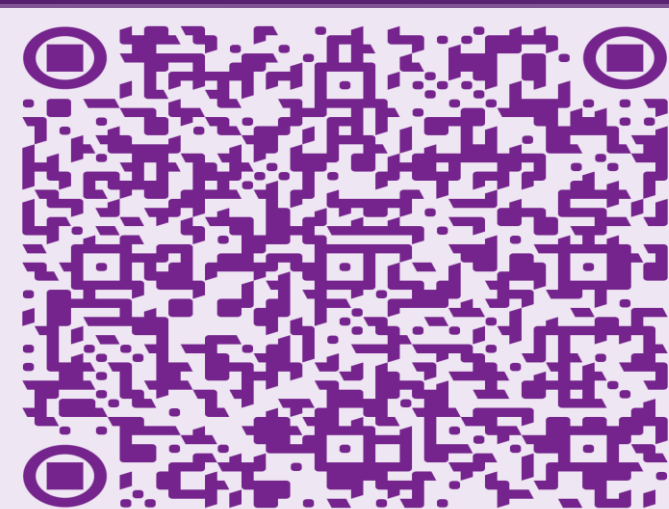
- Clinical relevance
Amyloid positivity + CDR-SB decline models in ADRC

- Multiplex panel
APOE4 + pTau-217 + GFAP + NfL vs genotype alone

References & Acknowledgements

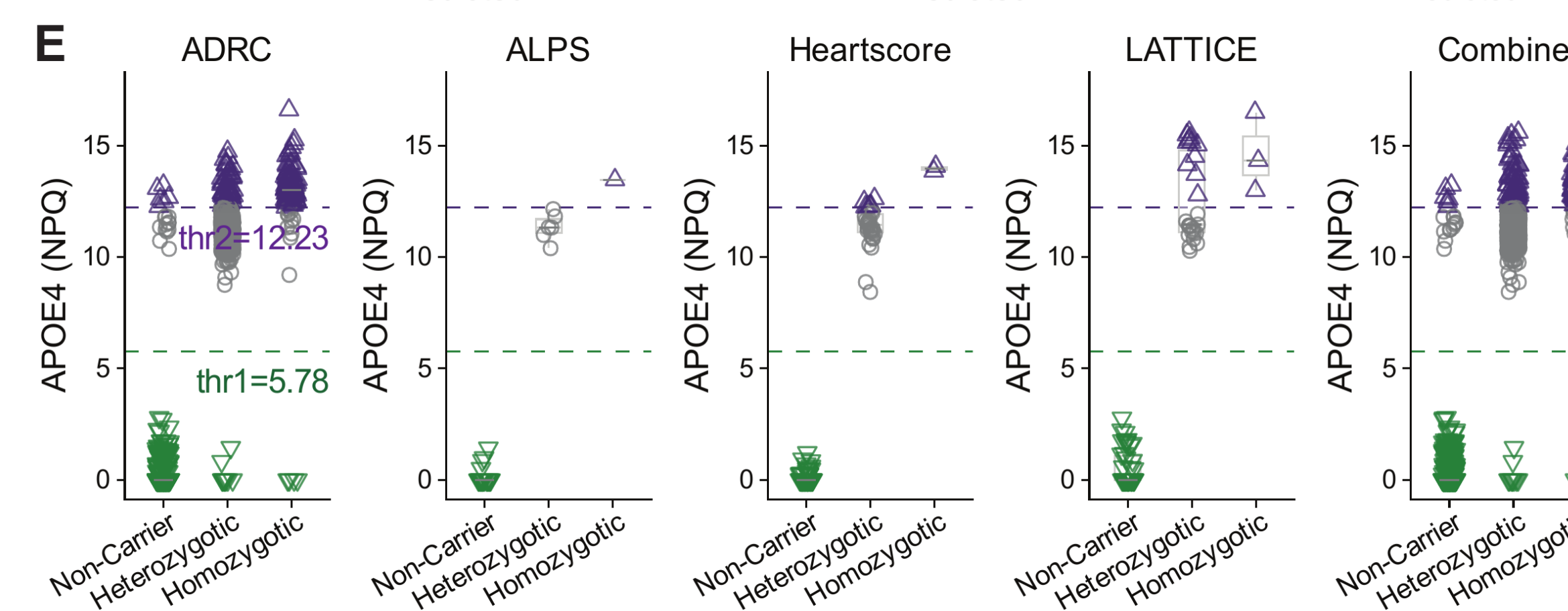
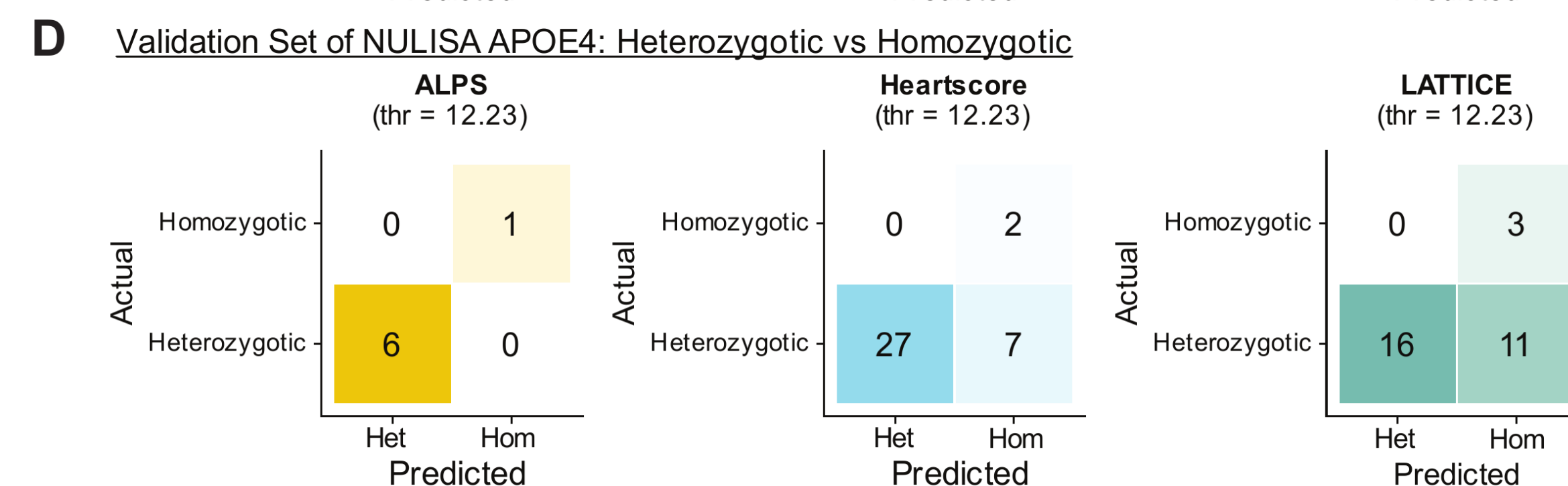
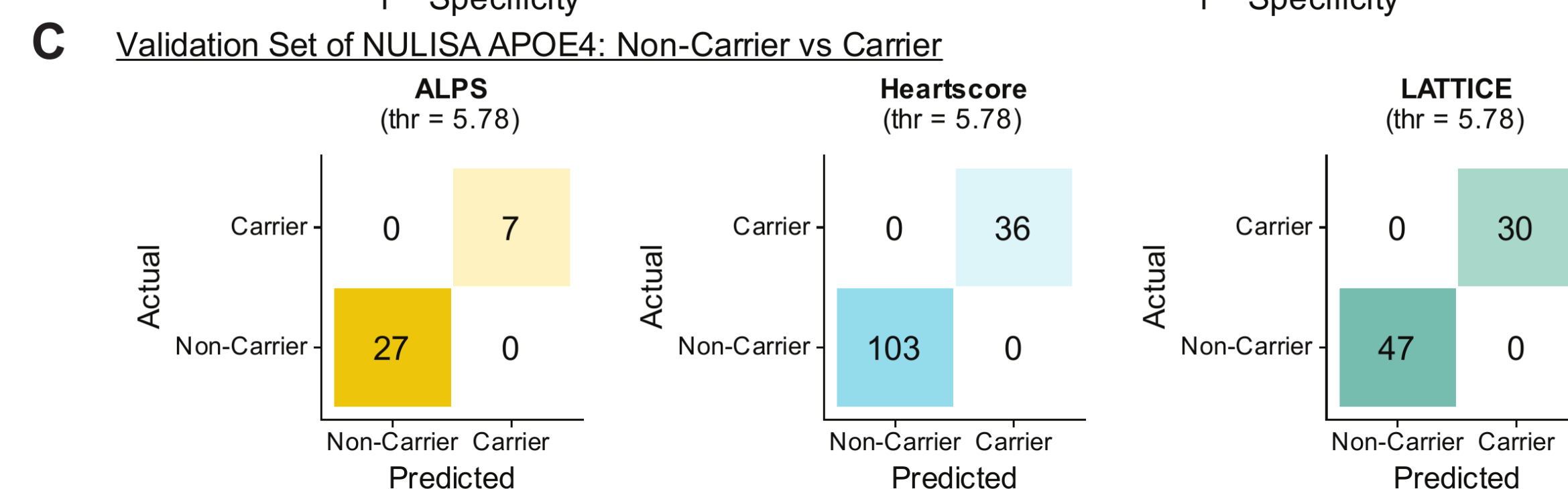
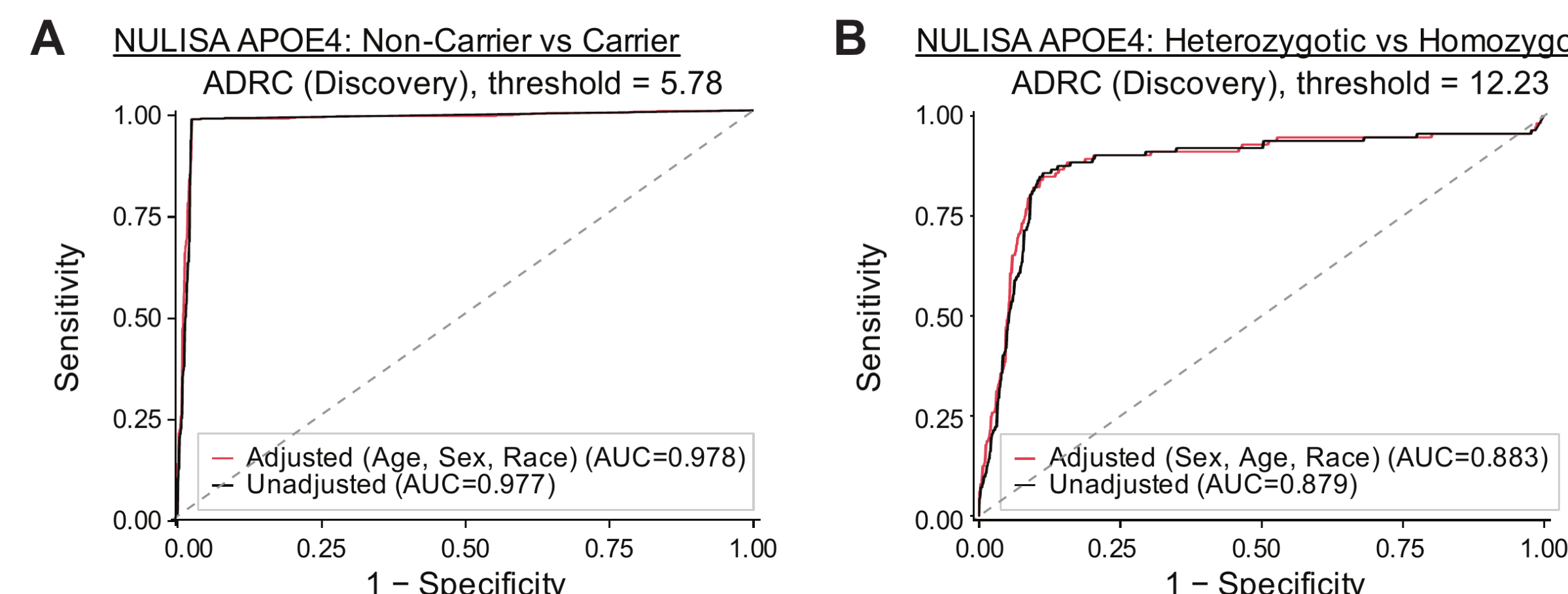
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Results

A. Plasma APOE4 recapitulates APOE ϵ 4 carrier status and gene dose

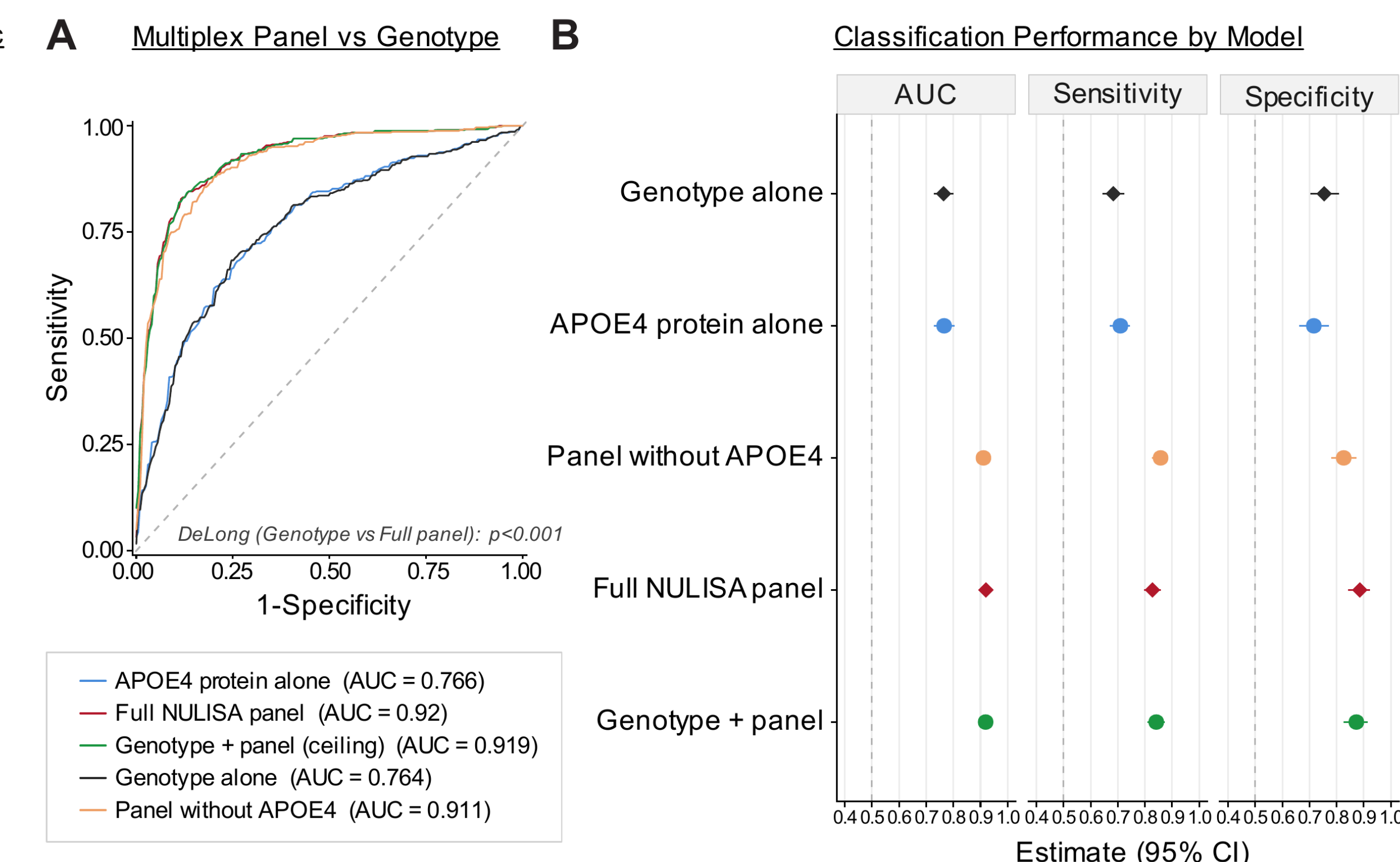


Carrier status: adjusted AUC 0.978; external validation shows no observed carrier misclassifications across ALPS, HeartSCORE, and LATTICE. Gene-dose threshold separates heterozygous vs homozygous carriers.

Conclusion

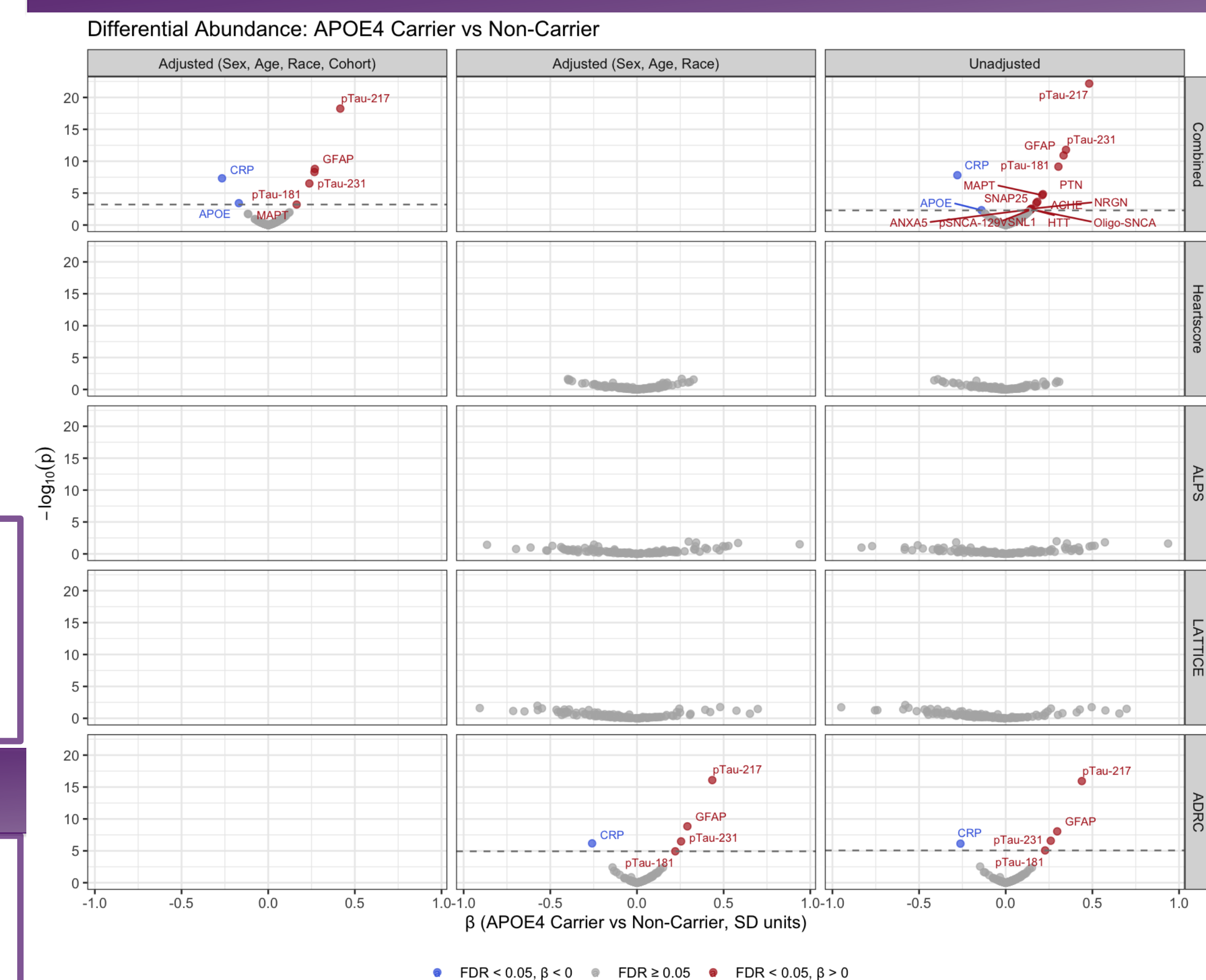
- Plasma APOE4 is a strong blood-based surrogate for APOE ϵ 4 genotyping
- Its main value appears to be genotype-level risk capture, not fine-grained risk stratification within established carriers
- A multiplex plasma panel provides more amyloid-risk information than genotype alone.

B. Multiplex proteotyping improves amyloid-risk assessment



The full NULISA panel outperforms genotype alone for amyloid prediction (AUC 0.920 vs 0.764). Adding genotype back does not meaningfully improve performance.

C. APOE4 carrier status links to AD-relevant proteomic shifts



Differential abundance supports molecular links between APOE4 carrier status and AD-relevant plasma markers, including tau/GFAP-related signals.