

# Integrated Blood Transcriptomic And Proteomic Analyses Identify Biomarkers Of Lecanemab Response In Early Alzheimer's Disease

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## Background

- Blood-based biomarkers may capture treatment-related biological changes and thereby improve mechanistic understanding and therapeutic monitoring in early Alzheimer's disease (AD). Lecanemab has been demonstrated to reduce cerebral amyloid- $\beta$  (A $\beta$ ) burden and slow clinical progression in individuals with early AD, yet the peripheral molecular signatures associated with therapeutic response remain incompletely characterized.

## Methods

- This study analyzed longitudinal clinical data and peripheral blood samples collected at baseline and follow-up from a cohort of individuals with early AD, including 30 patients treated with lecanemab and 30 untreated controls. All participants had been on stable oral anti-dementia medication for at least 4 weeks before enrolment. Whole-blood RNA sequencing was used for transcriptomic profiling, and serum proteomic profiling was performed using a high-resolution mass spectrometry platform. Utilizing longitudinal linear mixed-effects models, correlation analysis, mediation effect, and Mendelian randomization techniques, the molecular attributes of treatment responsiveness were discerned, and the biological processes associated with treatment response were elucidated through pathway enrichment analysis. A prediction model for treatment efficacy was developed using least absolute shrinkage and selection operator (LASSO) regression and logistic regression, with area under the receiver operating characteristic curve (AUC), sensitivity, and specificity as the main performance measures.

## Results

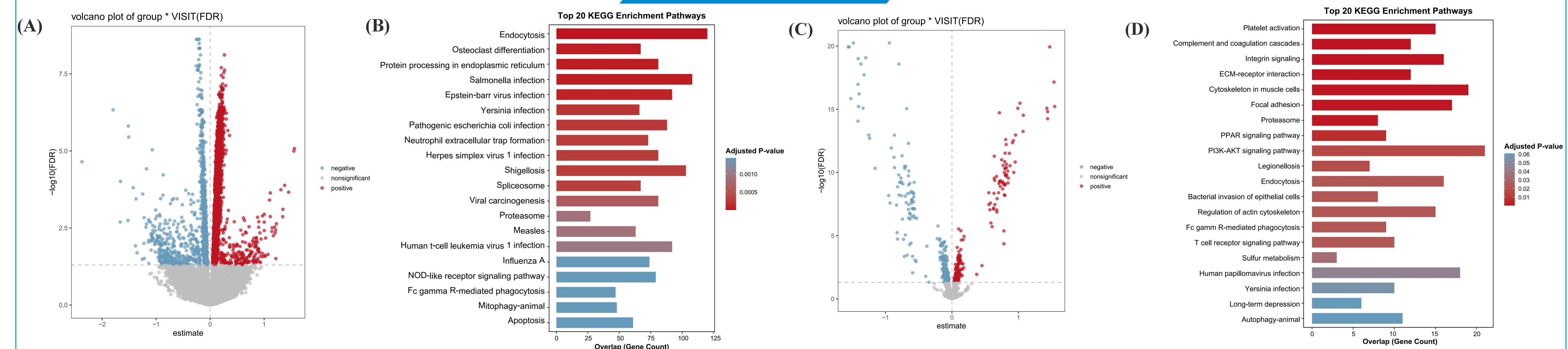


**Figure 1. Results of the linear mixed-effects model for transcriptomics and proteomics.**

(A) Transcriptomic interaction effect volcano plot. (B) Transcriptomic interaction effect KEGG pathway enrichment map. (C) Proteomic interaction effect volcano plot. (D) Proteomic interaction effect KEGG pathway enrichment map.

- Lecanemab treatment was significantly associated with dynamic changes in a panel of blood transcripts and serum proteins ( $p < 0.05$ ). Enrichment analyses showed concordance between transcriptomic and proteomic findings at both the molecular and pathway levels. Differentially expressed features were mainly enriched in pathways related to immune regulation, inflammatory responses, synaptic function, platelet-related processes, and cellular stress responses (Figure 1).
- Combined association and mediation analyses identified eight candidate biomarkers associated with changes in cognitive scores, including PLXNB2, BTK, and CMPK1. These markers appeared to partially mediate the relationship between lecanemab treatment and cognitive outcomes. A prediction model built on baseline molecular signatures achieved an AUC of 0.77 under leave-one-out cross-validation (Figure 2).

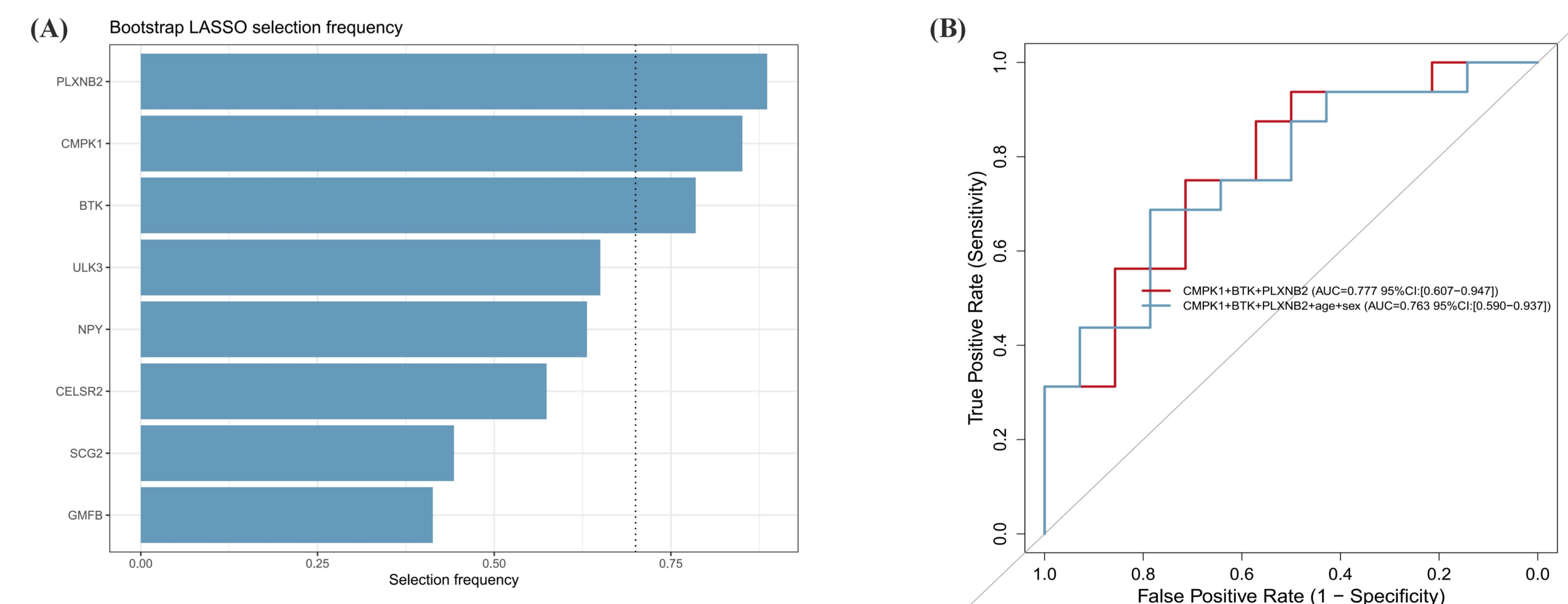


**Figure 2. Results of the baseline molecular feature prediction model.**

(A) Bootstrap LASSO selection frequency bar. (B) Receiver operating characteristic curve of the prediction model.

## Conclusion

- Peripheral blood molecules, including PLXNB2, BTK, and CMPK1, were closely associated with response to lecanemab and may serve as candidate biomarkers for dynamically monitoring treatment response. A predictive model based on blood multi-omics biomarkers may also provide a useful framework for evaluating lecanemab efficacy in the future.