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Machine Learning-Derived cfDNA Clinico-Methylation Signature Predicts Brain Metastasis Risk in Lung Adenocarcinoma

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Disclosure

- All authors are employees / hold shares of Guardant Health (Palo Alto, CA).

Disclosure

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ChatGPT (OpenAI) was used to support language refinement, content organization, and development of visual layouts for this poster. AI was not used to generate or analyze study data. All scientific content, analyses, interpretations, and final materials were reviewed and verified by the authors.

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Background and Methods

Brain metastasis (BM) remains an unresolved challenge in NSCLC. Despite its clinical impact, we lack reliable tools to identify patients at high risk for near-term BM.

We conducted a retrospective real-world study to develop a machine learning classifier predicting BM within 90 days of a Guardant360 Liquid assay (index test) in patients with lung adenocarcinoma (LUAD).



DISEASE BURDEN

- Brain metastasis (BM) occurs in a substantial proportion of NSCLC patients, with reported incidence around **24%** overall, **32%** in locally advanced NSCLC, and **37%** in advanced NSCLC.
- LUAD** patients are more prone to developing BM than non-LUAD.
- 10–20%** of NSCLC patients have BM at diagnosis, and up to **~40%** develop BM during the disease course.





CLINICAL CONSEQUENCE

- BM is associated with worse outcomes and often requires multidisciplinary management across neuro-oncology, radiation oncology, neurosurgery, and medical oncology.





GAP IN CURRENT WORKFLOWS

- Routine brain MRI surveillance is not recommended after curative-intent therapy for **stage I–III NSCLC**, and there are no recommended, established tools to identify patients at high near-term BM risk.
- Expert guidance in **unresectable stage IIb** NSCLC also notes that routine post-treatment brain imaging is not recommended, although baseline brain MRI is recommended for staging and CNS symptoms should trigger assessment.





There is an opportunity for a **blood-based risk stratification tool** to identify **LUAD** patients at elevated near-term BM risk who may benefit from prioritized brain imaging.

An Extreme Gradient Boosting (XGBoost) model integrated tumor fraction (TF), ~1,500 differentially methylated regions (DMRs), and clinical/demographic variables. Model performance was evaluated on a held-out test set using the area under the receiver operating characteristic curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Hierarchical clustering was used to evaluate co-methylation patterns among the highest-ranking methylation-associated genes.

Figure 1. Cohort Derivation and Rationale for the 90-Day Prediction Window

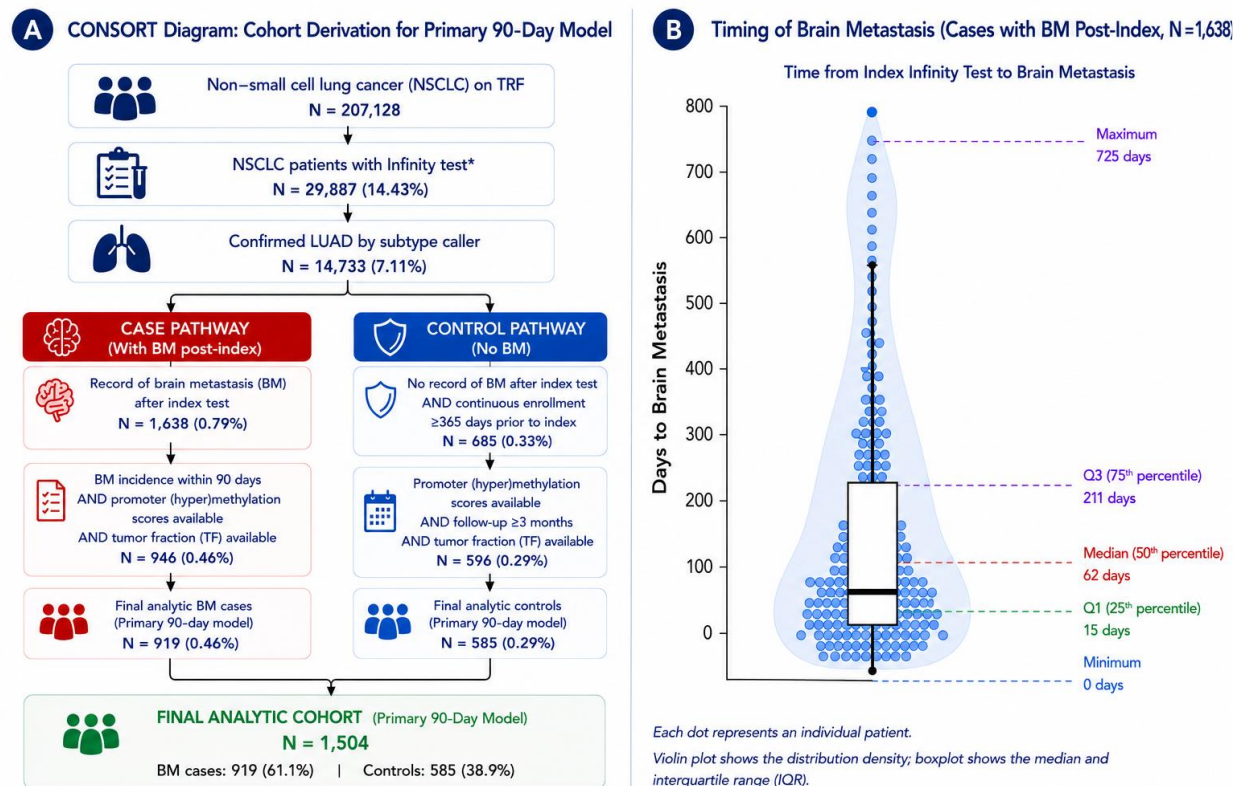


Figure 1. (A) CONSORT diagram showing derivation of the primary analytic cohort from a real-world claims-linked genomic database. (B) Distribution of time from the index test to BM among patients with post-index BM (N = 1,638), supporting evaluation of a 90-day prediction window.

Figure 2. Model Performance

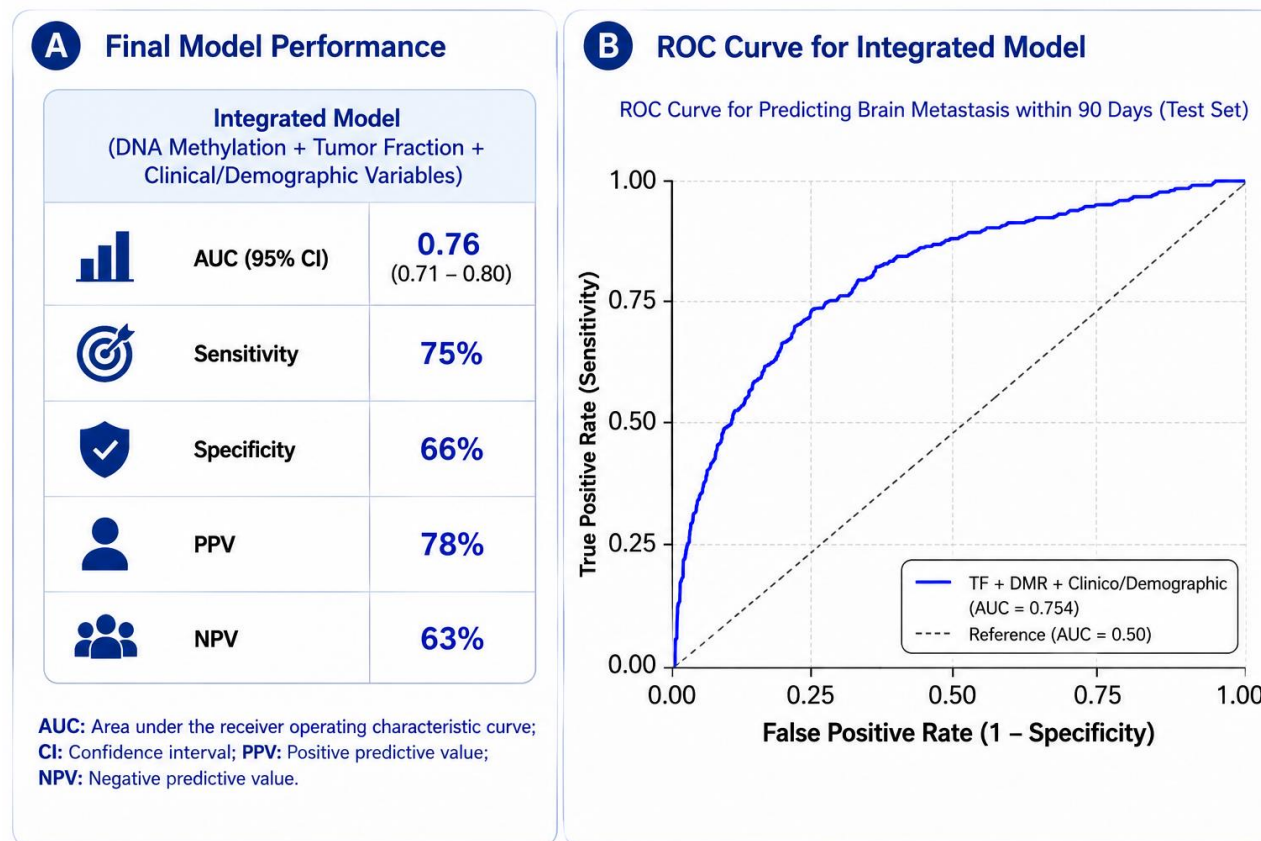


Figure 2. (A) Performance of the integrated XGBoost model combining tumor fraction, DNA methylation, and clinical/demographic variables for predicting BM within 90 days. **(B)** ROC demonstrating the performance for the integrated model.

Figure 3. Key Predictors and Biological Interpretation of BM Risk

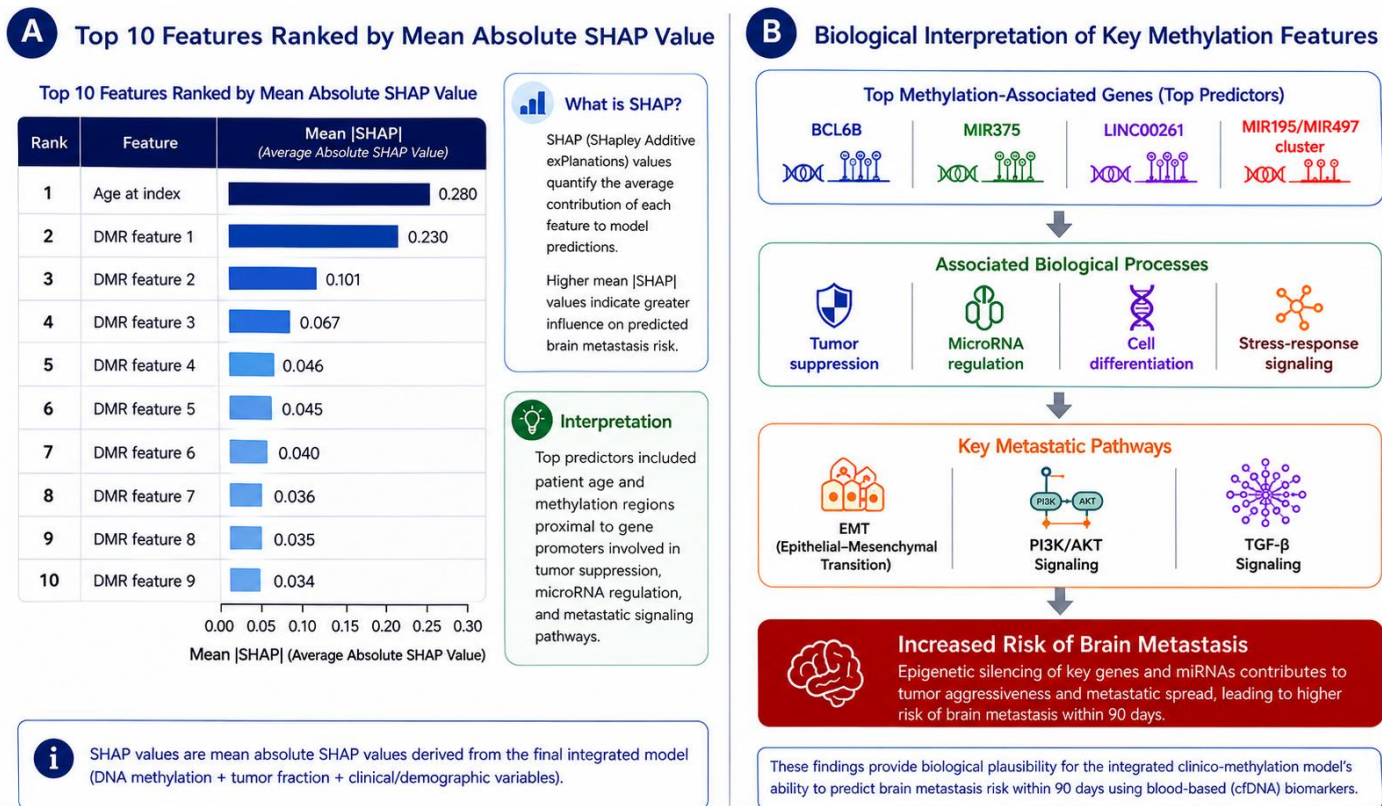


Figure 3. (A) SHAP analysis identified patient age and methylation-derived features as the strongest contributors to prediction of BM within 90 days. (B) The highest-ranking methylation-associated genes mapped to biological processes and metastatic signaling pathways associated with tumor progression.

Figure 4. Hierarchical Clustering of Top Methylation-Associated Genes

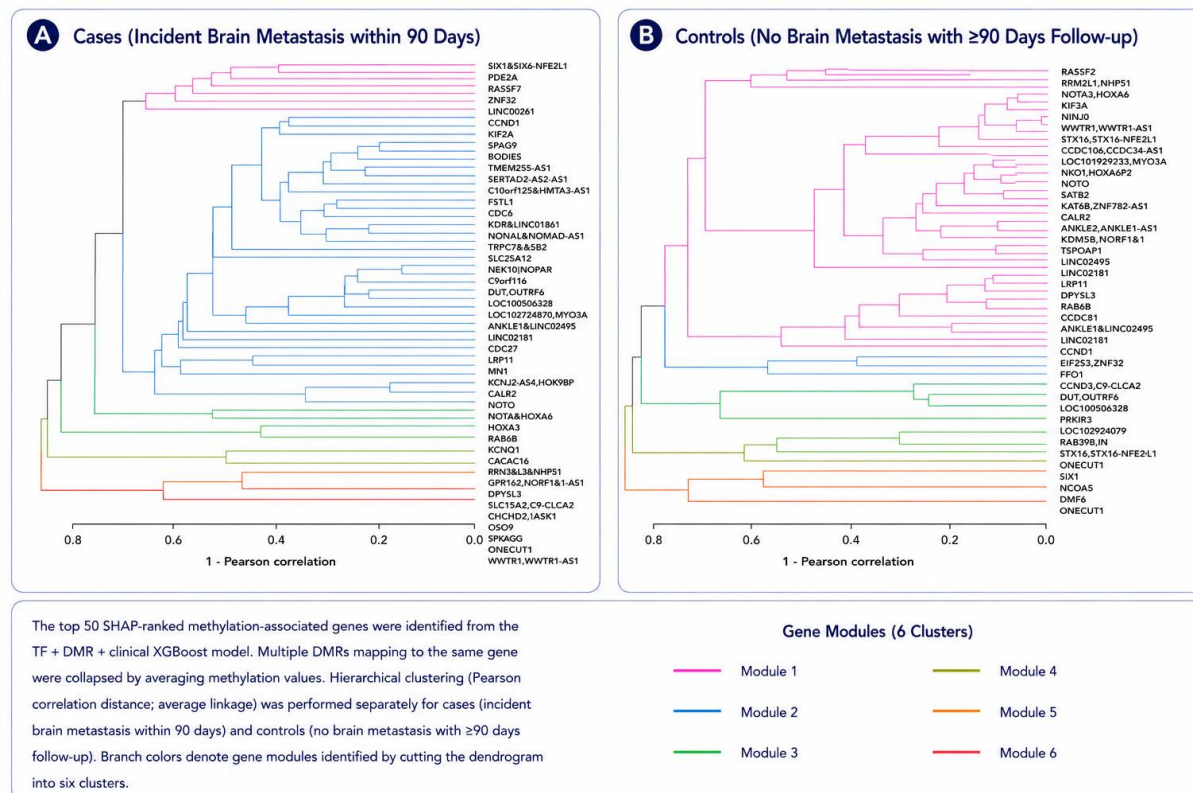


Figure 4. (A) Hierarchical clustering of the top 50 SHAP-ranked methylation-associated genes in patients with incident BM within 90 days of the index test. (B) Corresponding hierarchical clustering in controls without BM and ≥ 90 days of follow-up. Distinct co-methylation architecture suggests coordinated epigenetic programs associated with BM development.

Conclusions



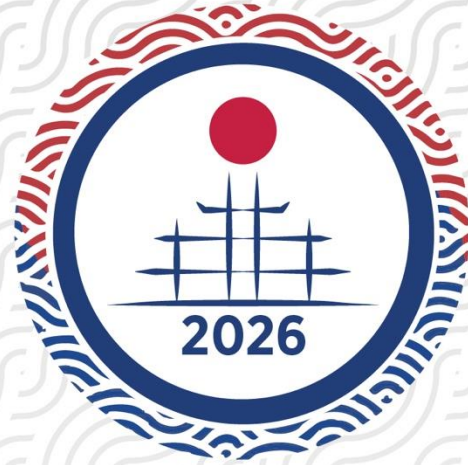
An integrated cfDNA clinico-methylation model demonstrated promising performance for predicting near-term BM risk



Methylation-derived biomarkers captured coordinated biological programs associated with tumor progression and metastatic dissemination, supporting prospective validation of blood-based approaches for personalized CNS surveillance



Future work will focus on model validation and evaluating how BM risk prediction can inform CNS imaging



Thank You.