

Systematic and Robust Prediction of Gene Expression Using Comprehensive Epigenomic Profiling of Plasma cfDNA

Khoi Nguyen^{*1}, Justin Finkle^{*1}, Anthony D'Ippolito^{*1}, Jonathan Beagan^{*1}, Aparna Gorthi^{*1}, Travis Clark¹, Amy Donahue¹, Baovy Tran¹, Tyrone Tamakloe¹, Charlene O'Brien¹, Michael Coyne¹, Jenna I. Wurster¹, Kristian Cibulskis¹, Corrie Painter¹, Mike Zhong¹, Humphrey Gardner¹, Jacob Berchuck², Jayne Stommel³, SMMART Clinical Trials Program³, Gordan Mills³, J. Carl Barrett¹, Matthew L. Eaton¹

¹Precede Biosciences, Boston, MA, ²Winship Cancer Institute of Emory University, Atlanta, GA, ³SMMART Clinical Trials Program, Knight Cancer Institute, Oregon Health & Science University, Portland, OR

BACKGROUND

Accurate prediction of RNA transcript levels from circulating tumor DNA (ctDNA) offers a promising approach for dynamic non-invasive cancer biomarker characterization and longitudinal monitoring. By leveraging epigenomic signals proximal to individual genes, we developed transcript level machine learning prediction models for breast and prostate cancer using simulated plasma and validated them in patient plasma.

METHODS and RESULTS

In breast cancer, our models predicted expression for a panel of 2622 key breast cancer oncogenes and transcriptional drivers in simulated plasma at 10% ctDNA or lower, enabling clinically relevant prediction of cancer gene transcription. At 10% ctDNA, we can evaluate all models in ~40% of stage IV patients, but many models remain performant at lower ctDNA levels, expanding the evaluable patient population.

These models are tuned to separate healthy plasma signal from cancer cells' contribution to the plasma. The panel is enriched for genes important for transcriptional regulatory identity and breast cancer subtypes, as well as targets for antibody drug conjugates (ADCs) and radio immune conjugates (RICs), including HER2, PSMA, Nectin-4, B7-H4, MET, and EGFR.

Our models demonstrated direct applicability in patient plasma with orthogonal validation. For example, they accurately predicted prostate cancer PSA and PSMA PET SUVmean, as well as breast cancer HER2, ER, and PR status. Additionally in a cohort of patients with matched tissue RNA-seq there was a strong correlation between RNA-seq and plasma-based predictions.

Further improvements were achieved with bespoke feature engineering and multi-gene aggregation. These strategies improved AUC for predicting HER2, ER, and PR IHC positivity in breast cancer, as well as the performance of our predictor for PSMA PET SUVmean. Similarly, for a multi-gene DLL3 predictor in lung cancer, we reduced the ctDNA threshold from 4% to 1.9% ctDNA by incorporating predicted expression of three highly correlated genes.

Figure 1. Epigenomic Platform

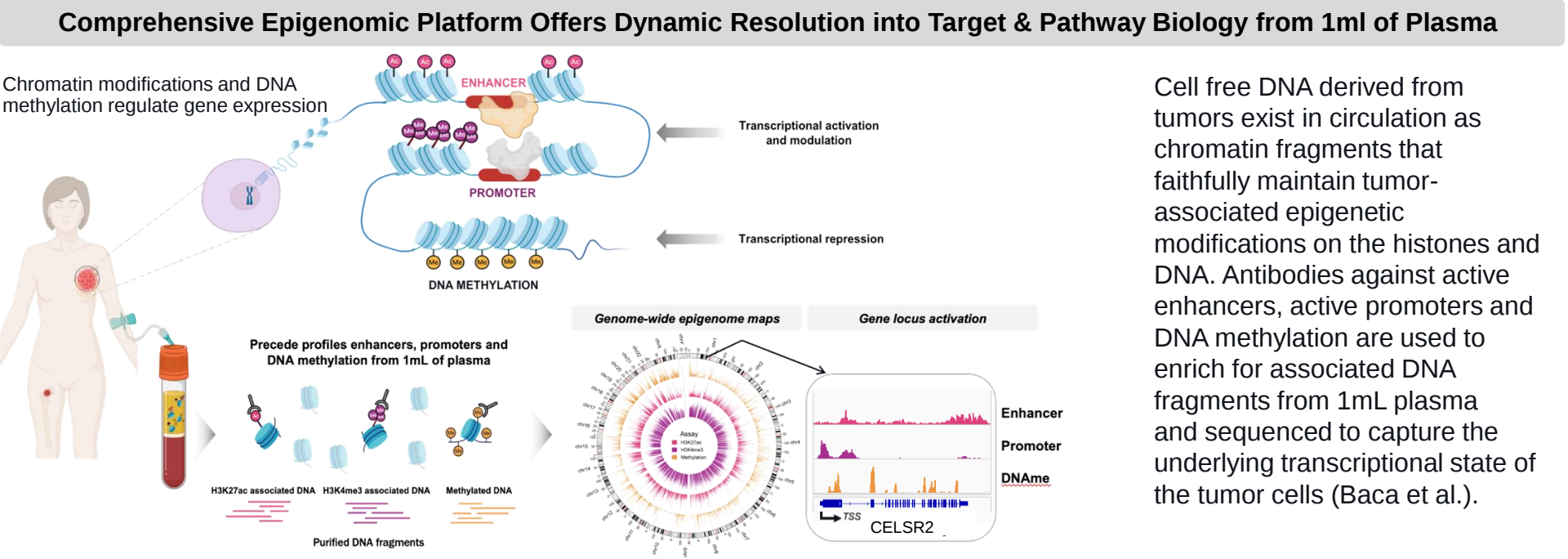
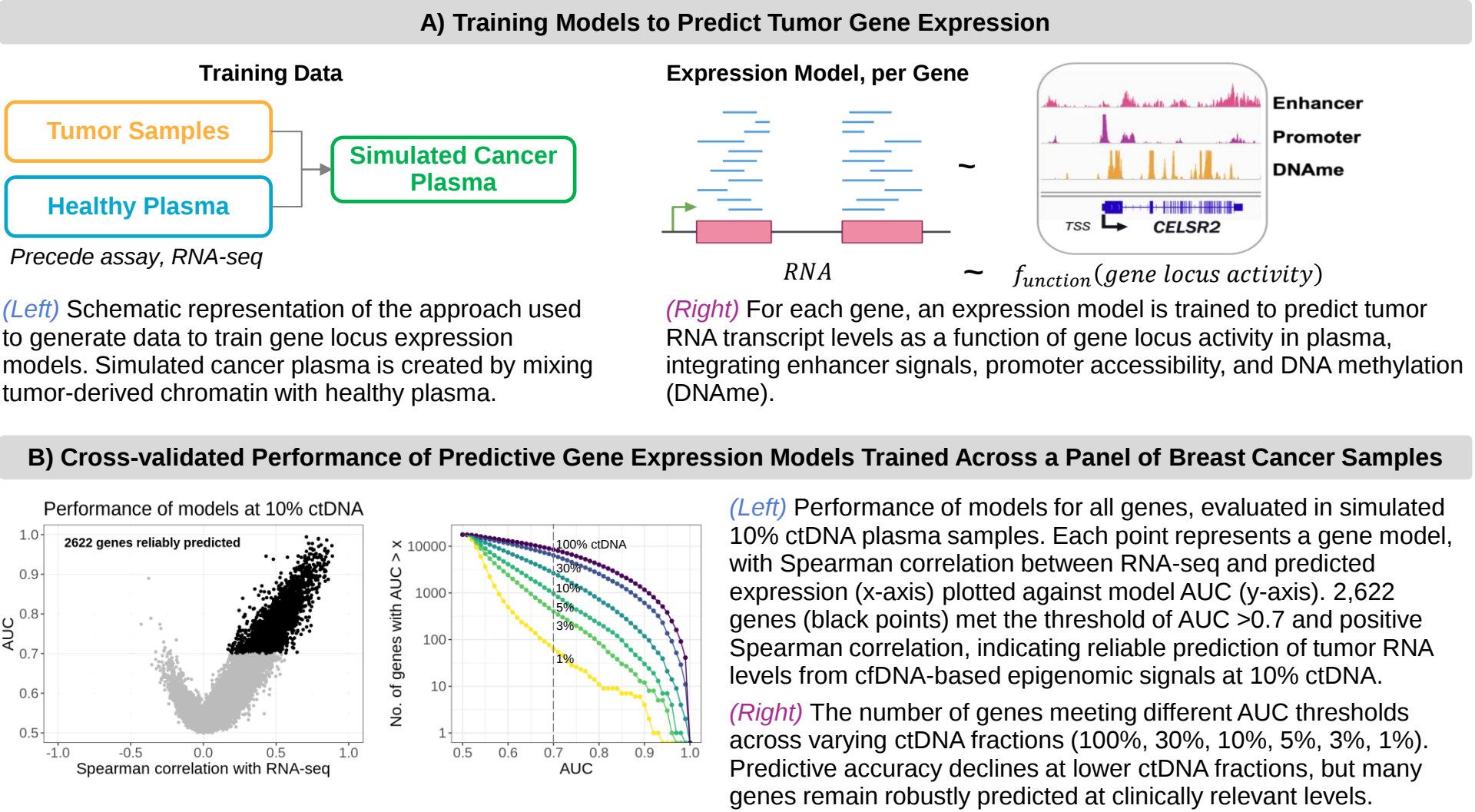


Figure 2. Training & Testing of Predictive Gene Locus Expression Models in Simulated Cancer Plasma



RESULTS

Figure 3. Gene Expression Predictions in Clinical Patient Plasma Validate in Tumor RNA-seq

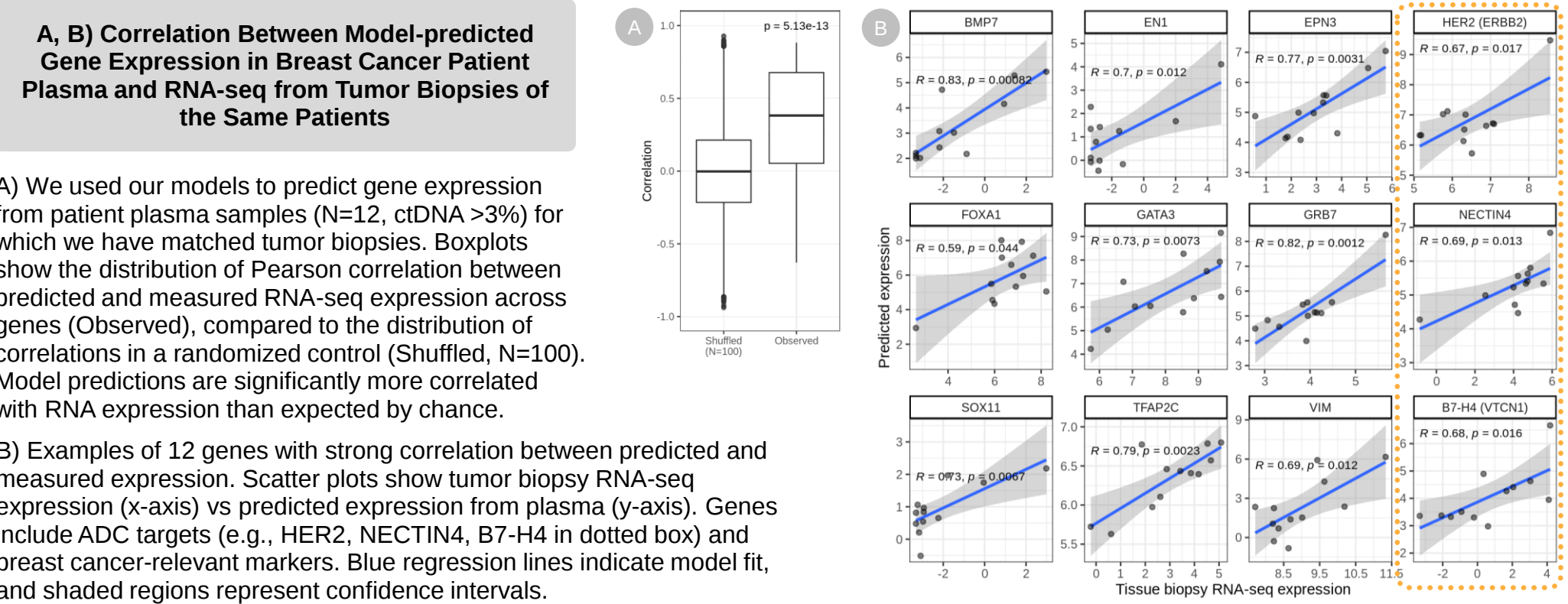
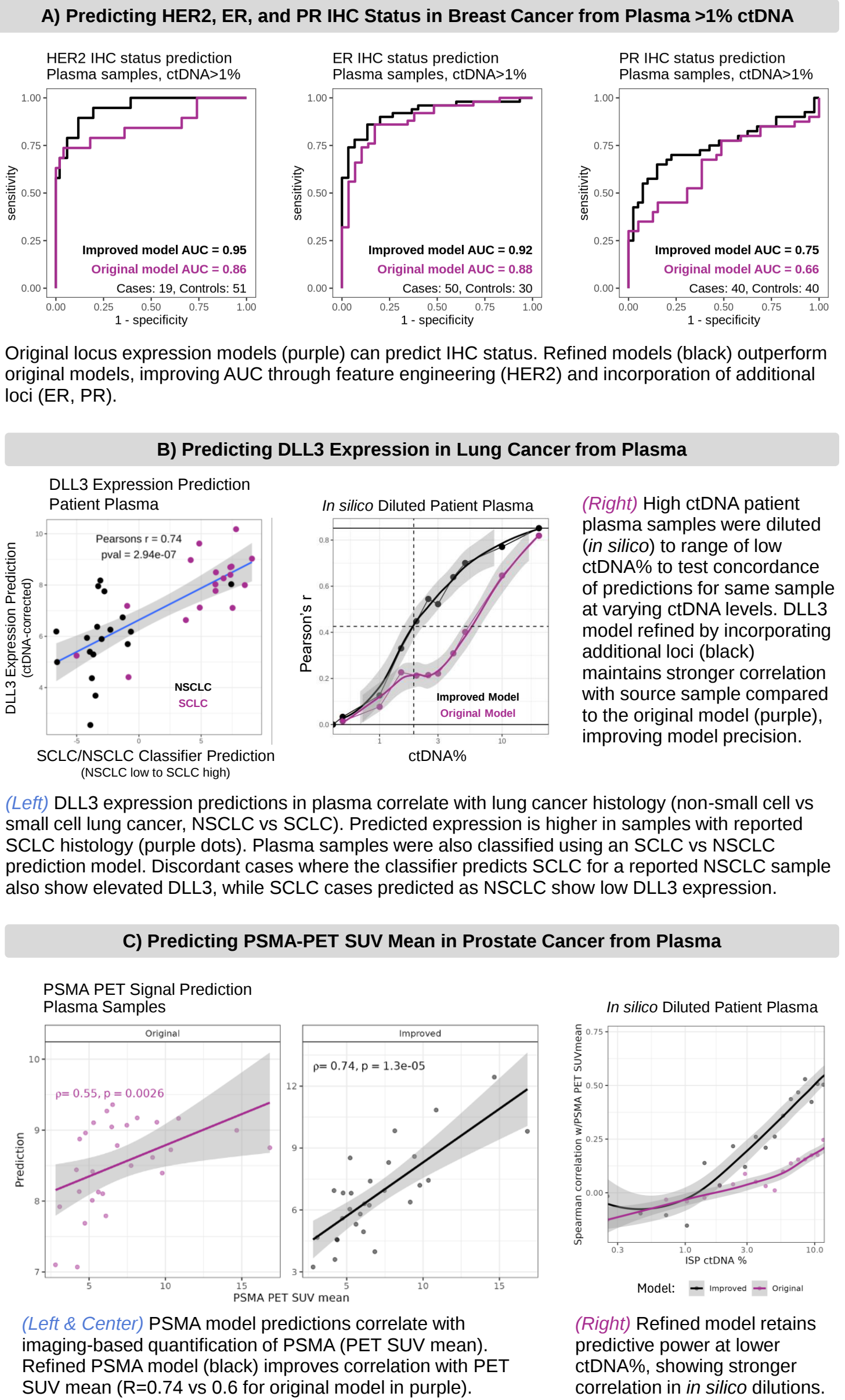


Figure 4. Development of Clinically Relevant Tests with Gene Expression Models



CONCLUSIONS

Comprehensive epigenomic profiling enables accurate prediction of tumor-specific RNA transcription in cfDNA, even at low ctDNA levels. This approach enhances ADC target profiling and enables tumor transcriptional profiling in patients from blood. Expanding beyond proof-of-concept models promises improved predictive accuracy at lower tumor fractions and broader applications in diagnostics and therapeutic targeting.