

Fragmentomics analysis of targeted hybrid capture NGS cfDNA gene panel data yields an orthogonal genomic dimension for developing a robust prognostic model for metastatic breast cancer patients

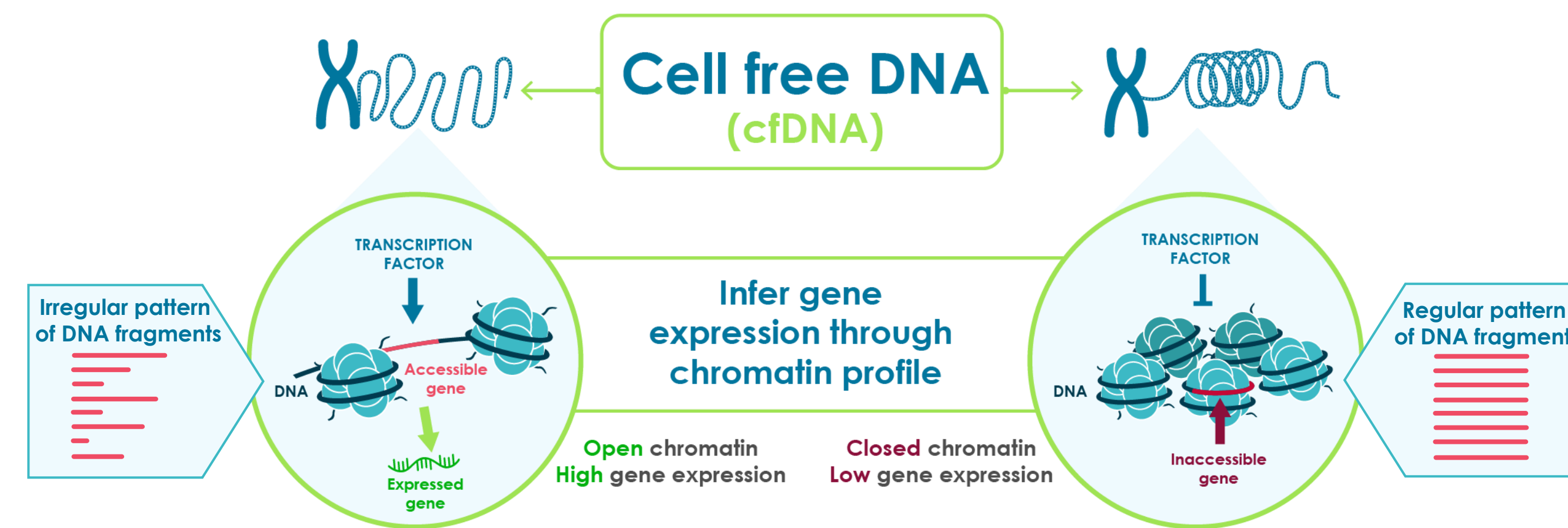
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Gregory M. Mayhew, Jonathan H. Shepherd, Jeff Burdine, Yoichiro Shibata, Gabriel V. Milburn, Michael V. Milburn, Kirk L. Pappan, James M. Davison, Kirk Beebe

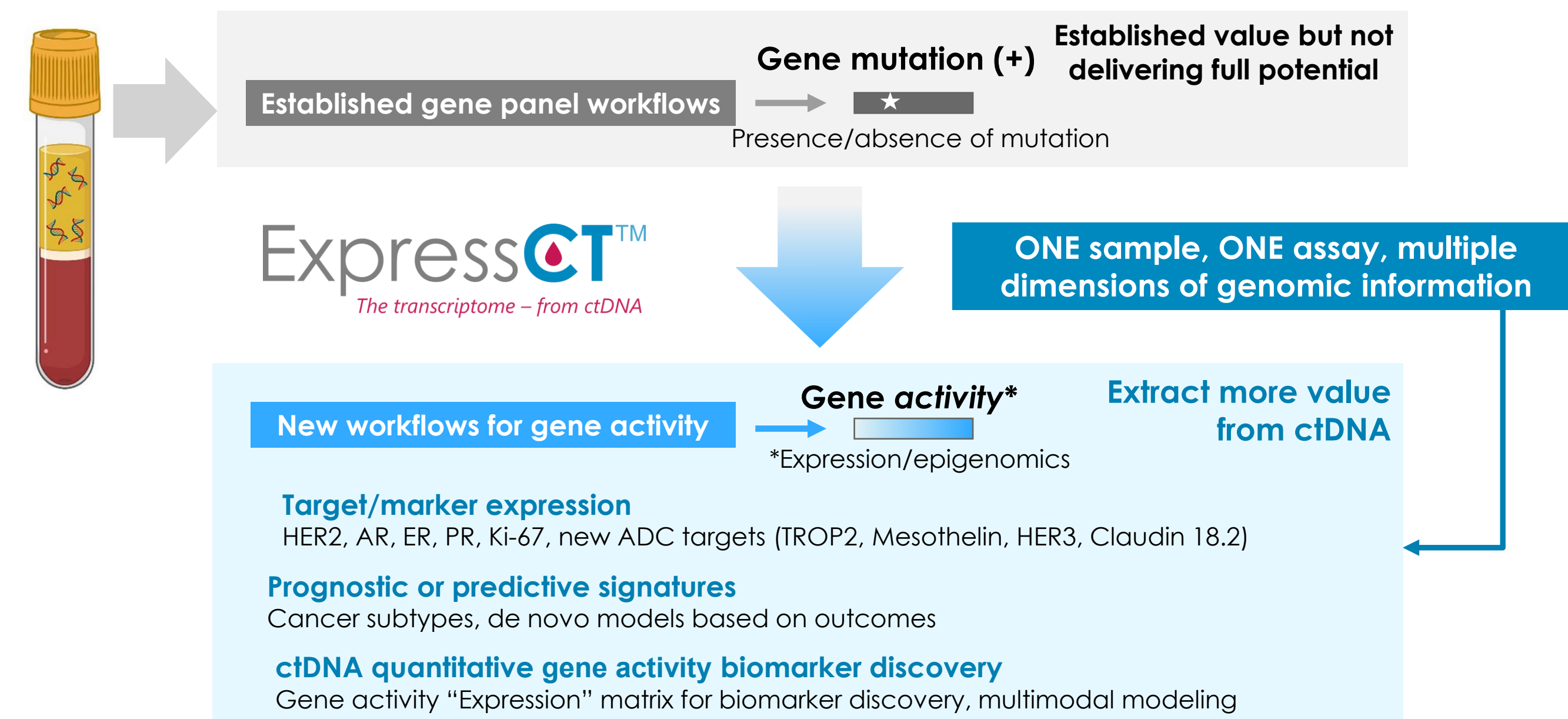
Background

Analysis of cfDNA fragment distributions, or fragmentomics, yields information about the transcriptional activity of genes but mostly has been applied to WGS and WES datasets.



ExpressCT Technology

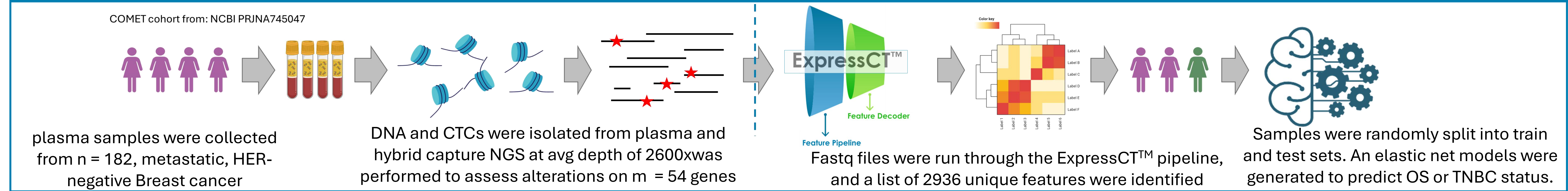
The widespread use of targeted hybrid capture NGS cfDNA gene panels provide a rich data source for mining orthogonal fragmentomic features for developing novel algorithmic signatures for prognosis and predicting response.



An additional layer of data with NO requirement for a new sample or separate assay

Here, we applied an uniquely developed fragmentomic computational method for hybrid capture panel data to a prospective study of HER2 negative, metastatic breast cancer patients, who were all treated with paclitaxel and bevacizumab.

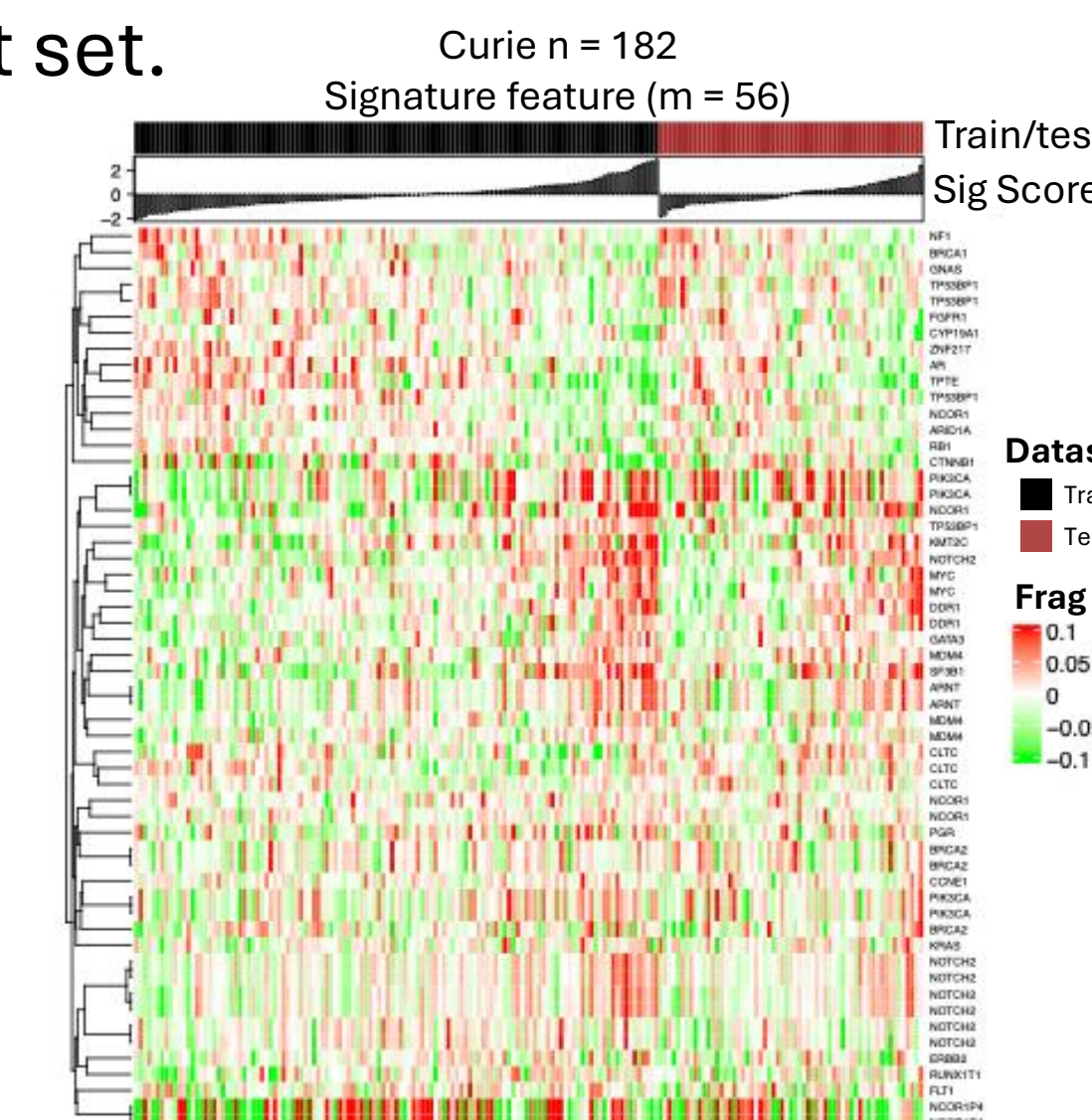
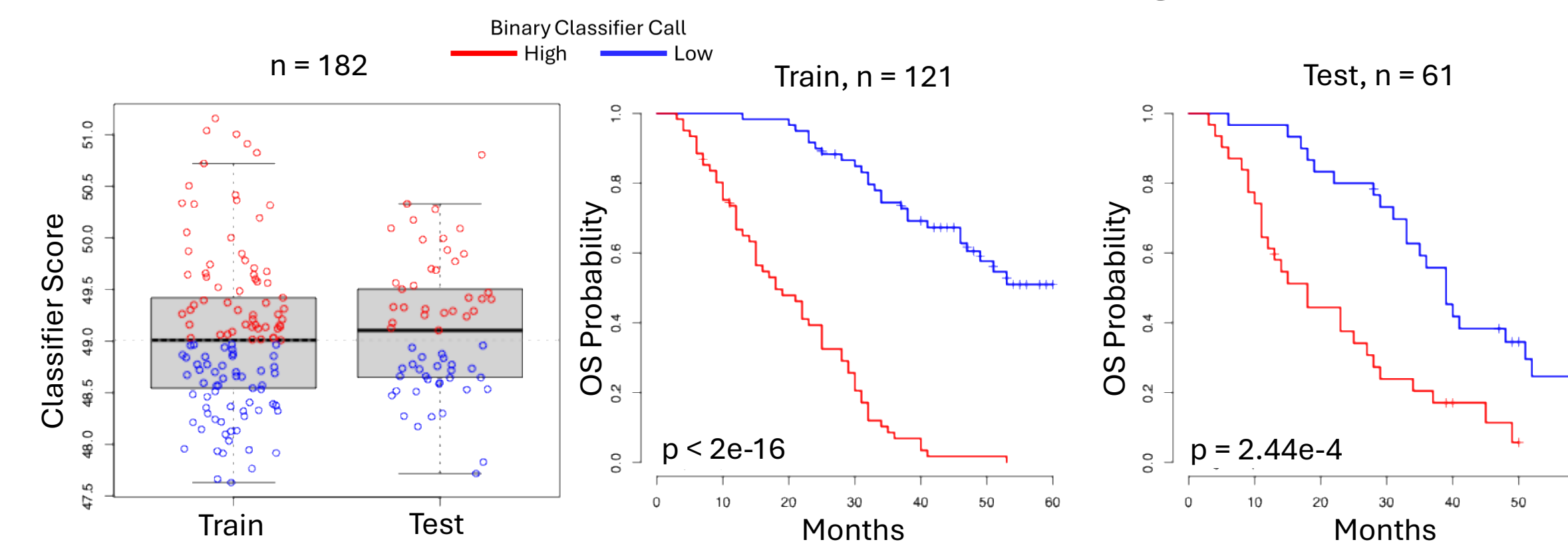
Study Design and Procedures



- Train and test sets were assessed for balance of age, HR status, metastasis site, CTCs and VAF.
- Cross Validation identified m = 56 features in OS model and m = 56 features in TNBC classifier
- Multivariate analysis was performed using CoxPH models to assess if the OS classifier performance was independent of age, TN status, tumor grade, etc.

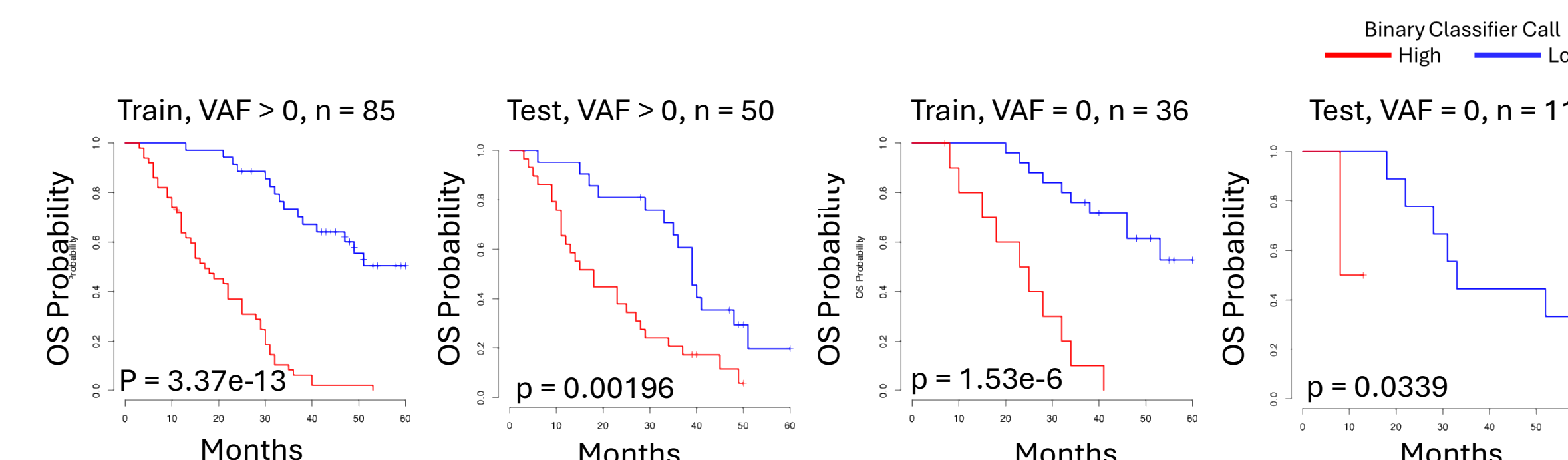
Prognostic classifier

An OS signature developed in the training set used 56 fragmentomics features and significantly identifies patients with worse OS in the left-out test set. Individual features that associate with survival are reproducible across samples (heatmap to right)



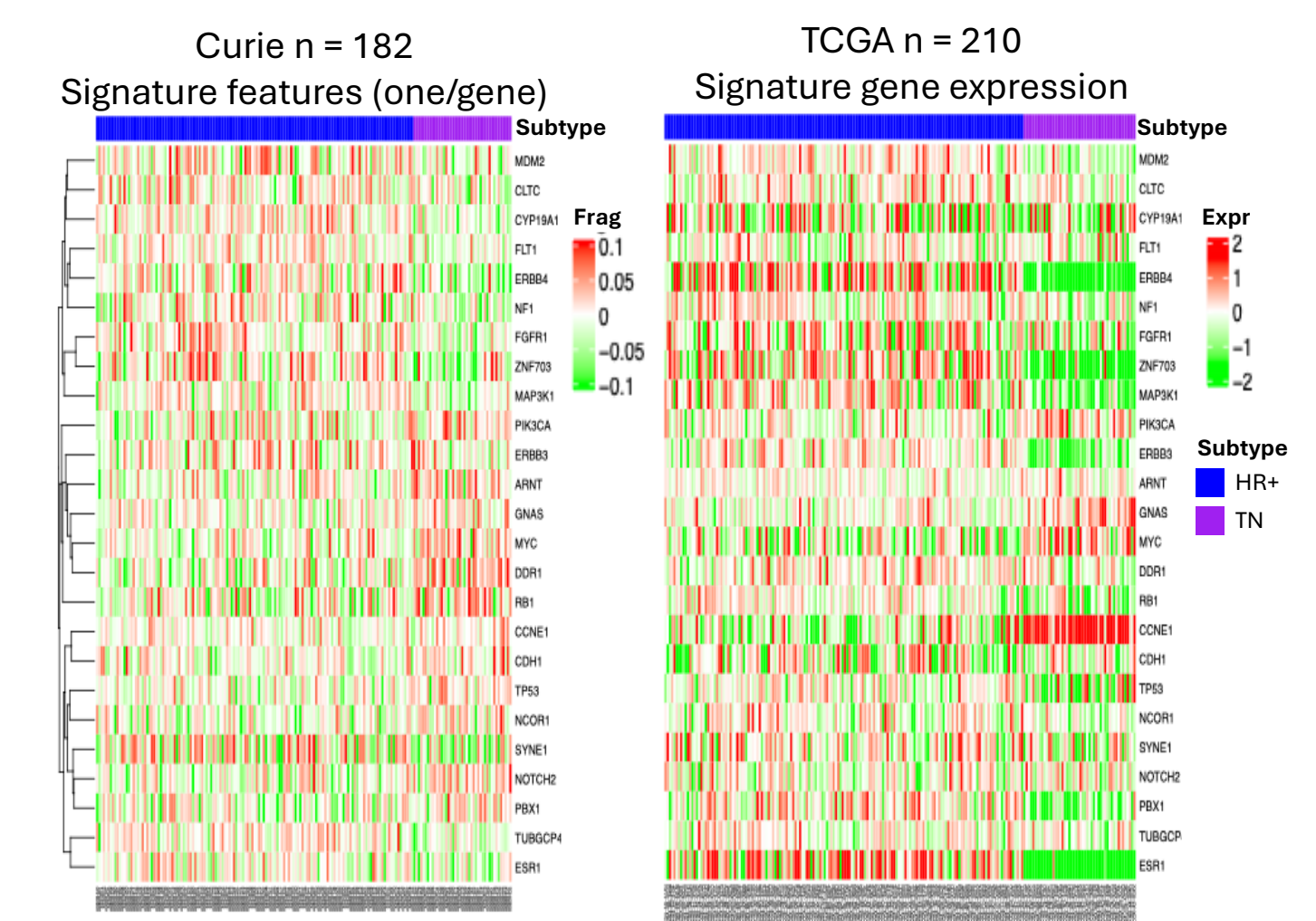
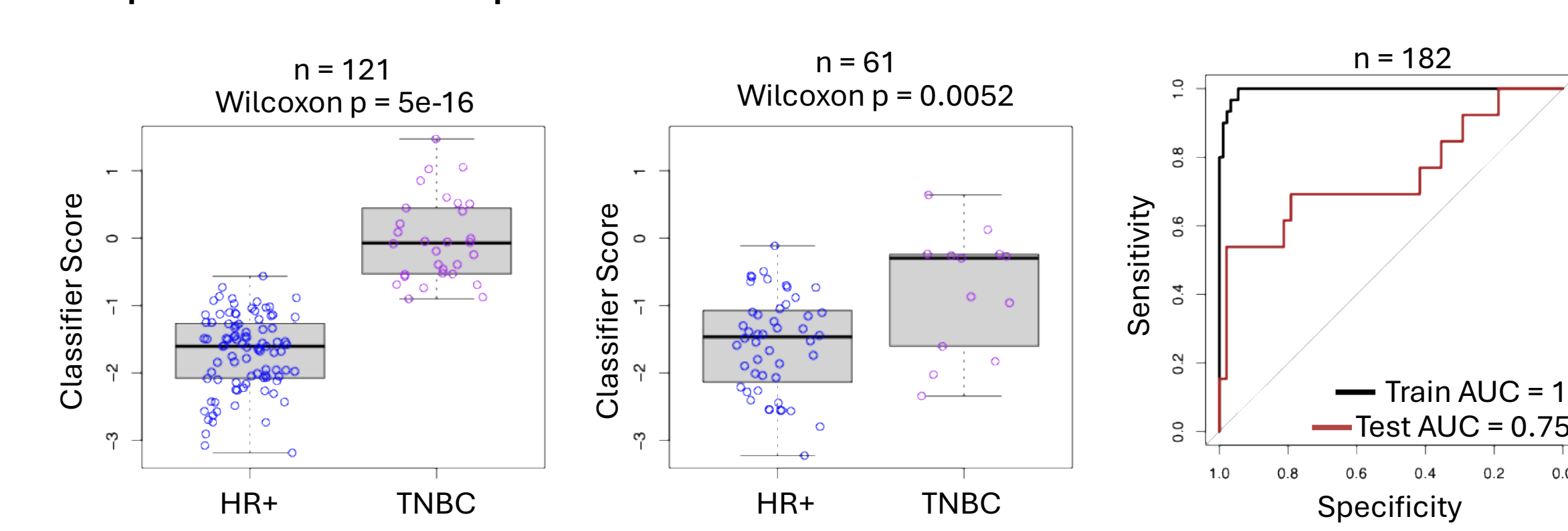
Performance by tumor content

The association between the signature and OS was uniform in low and high tumor content strata and significant.



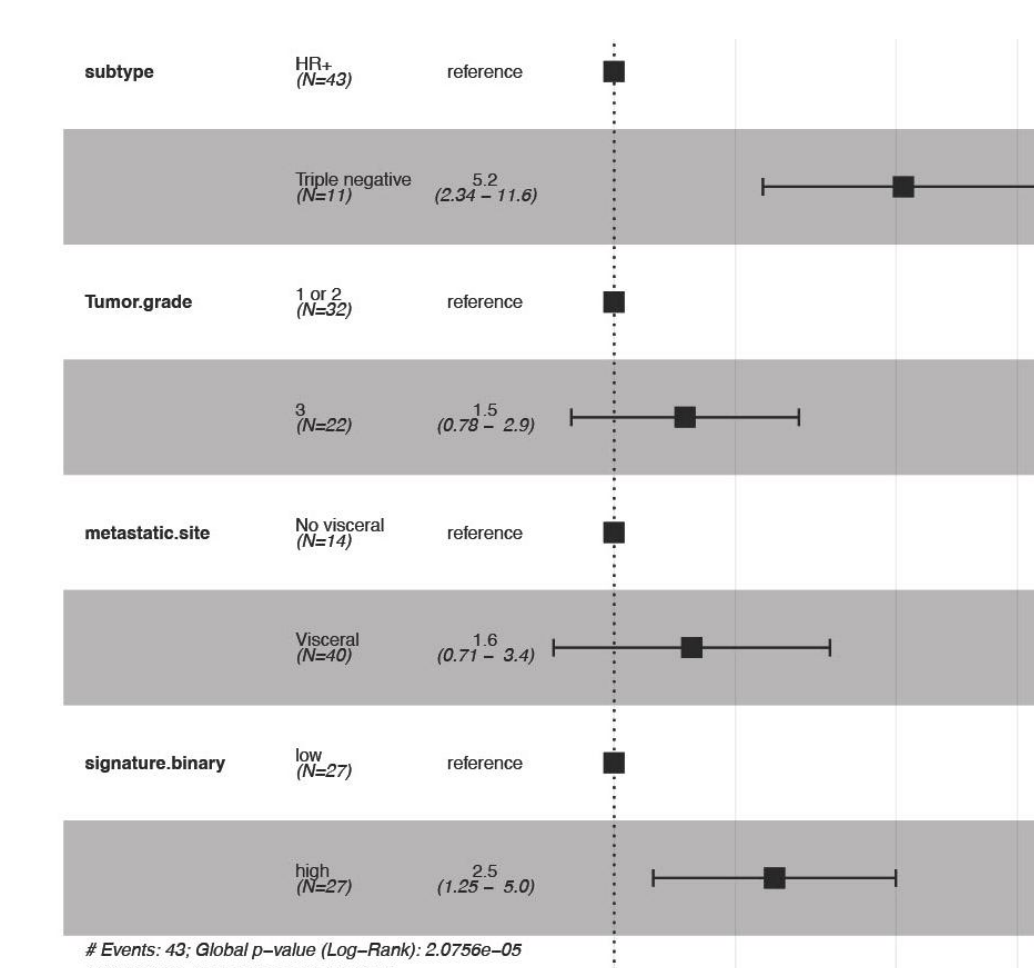
TNBC Classifier

The TN status signature developed in the training set used 56 fragmentomics features. In the test set, the signature was associated with TN status (Wilcoxon p-value = 0.0052) with an AUC of 0.75. Individual features that associate with TN are differentially expressed in a separate BC cohort



Multivariate OS Analysis

The addition of the fragmentomics signature to a multivariable OS model that already included parameters for TN status, tumor grade, and metastatic site significantly improved the model fit (LRT p-value = 0.009), with a signature hazard ratio of 2.50 (95% CI 1.25-4.99). CoxPH analysis was performed on the test set.



Conclusions

- This work demonstrates development of robust predictive models using cfDNA hybrid capture fragmentomic data even in a low tumor fraction setting
- These signatures could represent potential biomarkers that could assist in clinical decision making.
- Caveats include the use of a small dataset and could be improved upon by additional samples with similar criteria.
- This work also supports the possibility of retrospectively using any cfDNA panel sequencing for fragmentomics analysis to identify additional predictive biomarkers.