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Liquid biopsy determination of HER2 status in breast cancer: results from a novel epigenomic platform

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Background

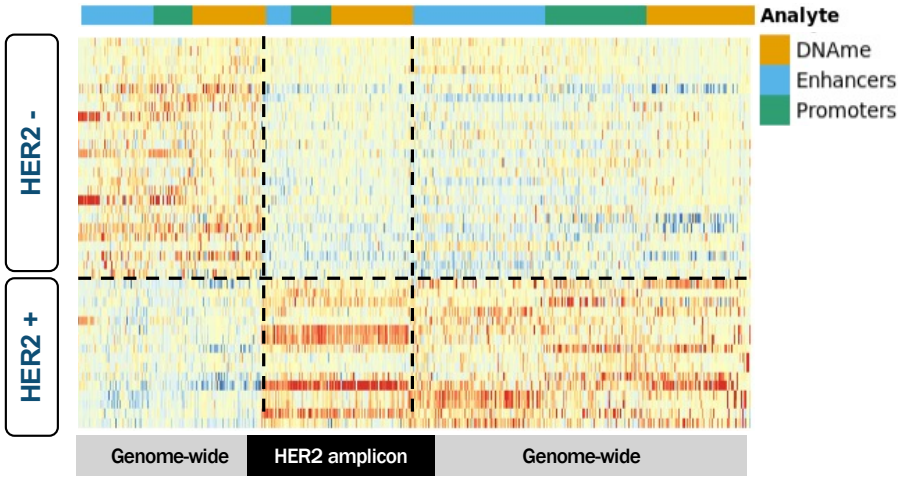
- HER2 status assessment relies on complex, tissue-dependent algorithm optimized for binary extremes: HER2+ vs HER2-
- Challenges in obtaining biopsies, inter- and intra-tumoral heterogeneity, lack of IHC scoring reproducibility in HER2 1+, 2+ necessitate novel biomarker approaches

Methods

- HER2 classifier developed via feature selection from epigenomically profiling breast cancer cell lines
- Cross-validated final classifier using standard Leave-one-Out scheme
- Profiled cfDNA from 1mL plasma drawn within six weeks of tumor tissue biopsy with pathologic HER2 and ER assessment from 130 patients with metastatic breast cancer from 1 academic center and 3 commercial biobanks

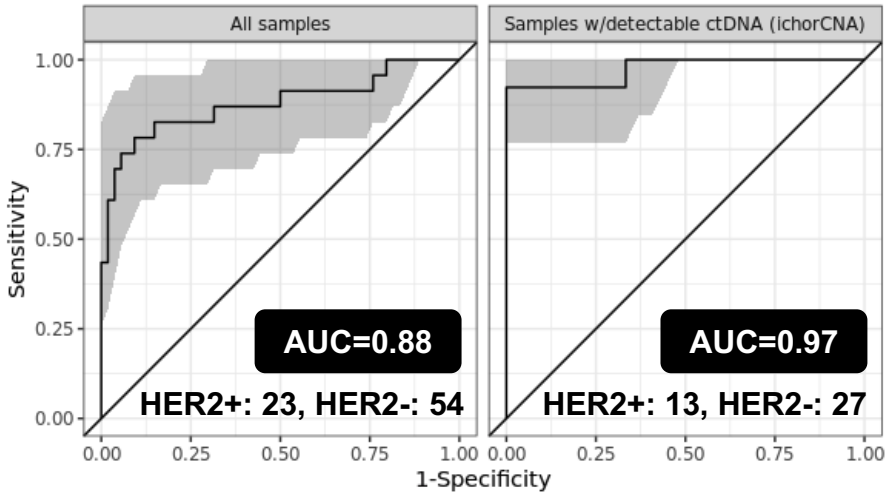
HER2 plasma-derived classifier correlates strongly with tissue phenotype in HER2 3+ vs 0

HER2 +/- differential loci detected in plasma



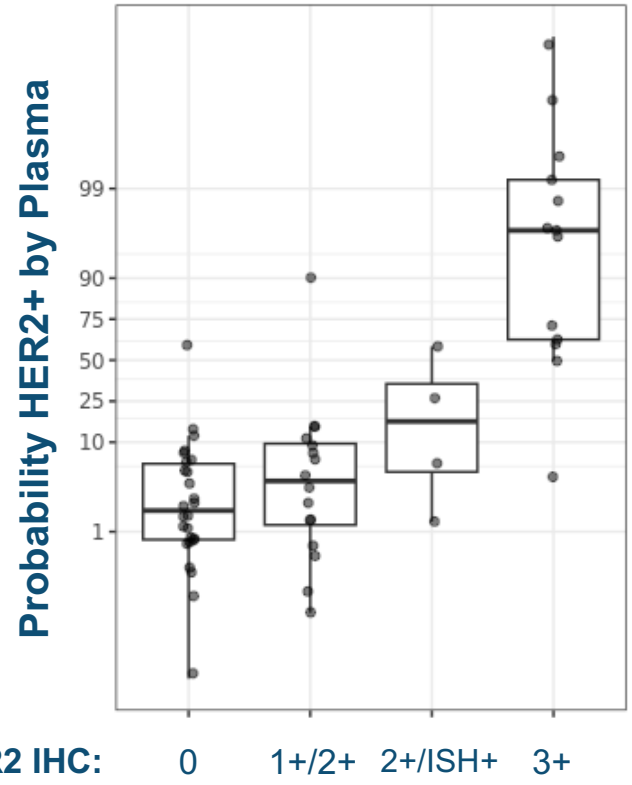
- Differential loci evident using enhancers, promoters, and DNA methylation
- Demonstrates genome-wide transcriptional biology and assesses HER2 status

Cross-validated HER2 classifier



- 91 loci used in HER2 3+ vs 0 multi-modal classifier
- 15 loci from HER2 amplicon
- 40% of loci derived from enhancer profiling

Application of HER2 3+/0 classifier to other HER2 states



- Efficacy of anti-HER2 ADCs in HER2-low population highlight significant need to identify patients
- Multi-analyte HER2 3+ vs 0 classifier provides early insight into potential for HER-low classification
- Further work will build on these results to develop a robust HER2-low classifier
- Ultimately, predictive value of the biomarker will be the gold standard to demonstrate clinical utility

In Conclusion

- Promising proof-of-concept from a **novel liquid biopsy approach** profiling tumor genome-wide transcriptional regulation from **1mL plasma**
- Given evolution of disease over time, potential to non-invasively reveal MBC biology in manner is potentially high impact, beyond HER2 status assessment
- Potential as a minimally-invasive means to assess and longitudinally monitor HER2 status in patients with MBC, with **AUC 0.97** from plasma with detectable ctDNA
- Limited by retrospective nature
- HER2 low and ER classification is ongoing, with promising ER results, **AUC 0.90** from plasma with detectable ctDNA (see virtual poster, **PS06-07**)
- Future work to include evaluation in additional cohorts and prospective application of biomarker