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Impact of race on BluePrint genomic subtyping in HER2+ breast cancer

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Background

- Breast cancer (BC) is the leading cause of cancer-related deaths in Black women, who are 41% more likely to die from BC than White women[1].
- We've recently reported that Black women have a significantly greater proportion of hormone receptor-positive (HR+) tumors further classified as Basal-Type with BluePrint genomic subtyping, which may contribute to their worse outcomes[2,3].
- Here, we evaluated whether there were differences in tumor genomics among patients with clinically assessed HER2+ (cHER2) tumors between Black and White women.

Methods

Patients: This study includes 204 women with stage I-III cHER2 BC who received MammaPrint (MP) and BluePrint testing and are participants of the retrospective BEST study (R01CA204819) at Vanderbilt University Medical Center, or prospective observational FLEX study (NCT03053193). Patients were treated according to IHC/FISH classification per NCCN guidelines. White women within FLEX were matched by age, tumor and node status and included as a reference group.

Molecular classification: MP classifies tumors as having a High or Low Risk of distant metastasis[4]. MP High Risk tumors can be further stratified as High 1 or High 2, where patients with High 2 tumors have demonstrated greater chemo-sensitivity than High 1 in the I-SPY2 trial[5,6]. BluePrint classifies tumor molecular subtypes as Luminal-Type (gLuminal), HER2-Type (gHER2), or Basal-Type (gBasal)[7]. MP and BluePrint further stratify Luminal tumors as Luminal A (MP Low Risk) or Luminal B (MP High Risk)[4-5,7].

Statistical analysis: A two-tailed proportional z-test was used to assess differences in molecular subtype and treatment response.

Whole transcriptome analysis: Limma R package was used for differential gene expression analysis (DGEA). Significant differentially expressed genes had an adjusted p-value < 0.05 and absolute log2 fold change > 1. Gene set enrichment analysis (GSEA) was performed with fgsea R package using Hallmark gene sets from the human MSigDB. Significant pathways had an adjusted p value < 0.05.

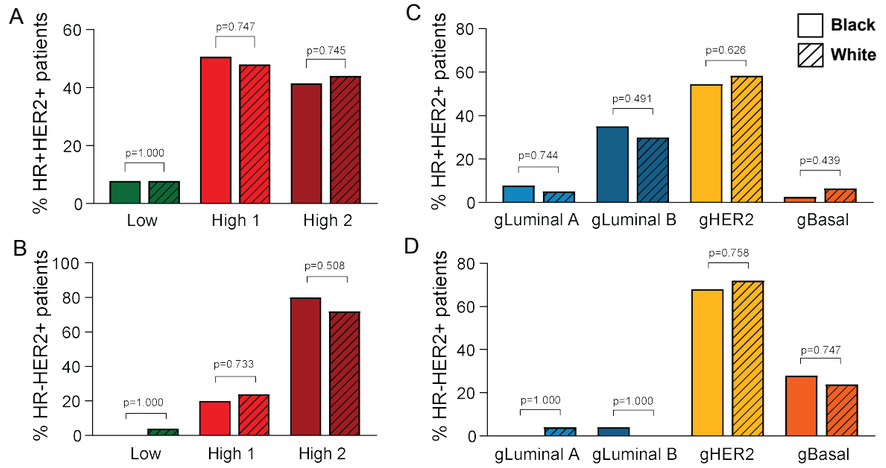
Results

Table 1. Clinical characteristics

	Black (n=102)	White (n=102)
Age, median (SD)	48 (13.7)	48 (12.4)
Menopausal status		
Pre-/peri-	55 (53.9)	46 (45.1)
Post-	44 (43.1)	49 (48.0)
Unknown	3 (2.9)	7 (6.9)
Tumor grade		
G1, Low	6 (5.9)	6 (5.9)
G2, Intermediate	29 (28.4)	42 (41.2)
G3, High	63 (61.8)	52 (51.0)
GX, Unknown	4 (3.9)	2 (2.0)
Clinical subtype		
HR+HER2+	77 (75.5)	77 (75.5)
HR-HER2+	25 (24.5)	25 (24.5)

Numbers presented as n (%), unless otherwise specified.

Figure 1. Frequency of (A,B) MammaPrint risk category and (C,D) BluePrint molecular subtype among Black and White women with HR+HER2+ and HR-HER2+ tumors.



- Of 102 Black women with cHER2 BC, 59 had gHER2, 34 had gLuminal and 9 had gBasal tumors, and of 102 White women, 63 had gHER2, 28 had gLuminal and 11 had gBasal tumors.

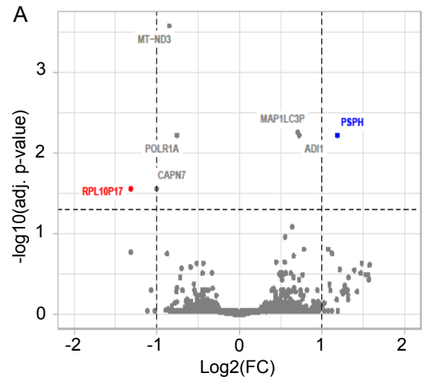
  There were no significant differences in the frequency of MammaPrint risk or BluePrint subtype by race among cHER2 tumors (**Figure 1**).

- Few differentially expressed genes and gene sets were identified between Black and White women with HR+HER2+ but not HR-HER2+ tumors (**Figure 2**).

- Among Black women with neoadjuvant treatment response data, 5 of 13 with gHER2 tumors achieved a pathologic complete response (pCR) compared to 11 of 15 among White women.

  When stratified by HR status, 4 of 10 Black women and 9 of 12 White women had a pCR. Similarly, 1 of 3 Black women with HR- tumors and 2 of 3 White women achieved a pCR (**Table 2**).

Figure 2. DGEA comparing (A) HR+HER2+ and (B) HR-HER2+ tumors classified as genomically HER2-Type among Black versus White women. Significant gene sets identified among patients with HR+ tumors are listed in table.



Significant pathways upregulated in Black women	Adj. p-value
IFNγ response	1.27E-09
IFNα response	7.69E-09
MTORC1 signaling	1.55E-04
Allograft rejection	0.004
MYC targets_V1	0.004
Protein secretion	0.006

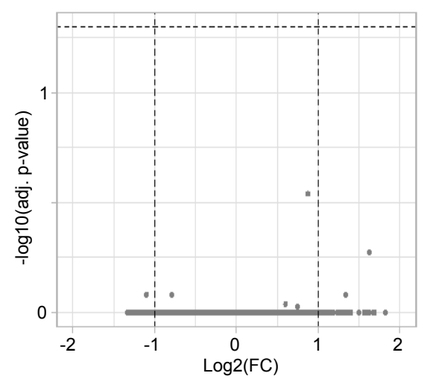


Table 2. Treatment response among patients with genomically HER2 tumors by race.

Clinical subtype	Race	Patients with pCR	Total patients
HR+HER2+	Black	4	10
HR+HER2+	White	9	12
HR-HER2+	Black	1	3
HR-HER2+	White	2	3

Number of patients with treatment response were too small to compare statistically.

Conclusions

In this study, BluePrint consistently further stratified heterogeneous cHER2 tumors, independent of race. Unlike our observations in HR+HER2- tumors, these data suggest that race may not influence the underlying biology of cHER2 tumors. The rate of further classification with BluePrint among cHER2 tumors was comparable to NBRST[8] and APHINITY[9], which demonstrated that patients with gHER2 tumors benefitted most from dual HER2-targeted therapy.

The pCR rates to neoadjuvant therapy appear lower in Black patients compared to White patients with gHER2 tumors. These data are limited by sample size and should be confirmed with a larger cohort; however, they are in line with a recent study showing Black women with cHER2 tumors had lower pCR rates than White women[10].

References

1. Giaquinto et al. CA Cancer J Clin, 2022.
2. Reid et al. JCO, 2022.
3. Reid et al. SABCS 2021.
4. Van't Veer et al. Nature, 2002.
5. Haan et al. Genes Chrom Cancer, 2022.
6. Wolf et al. NPJ Breast Cancer, 2017.
7. Krijgsman et al. BCRT, 2012.
8. Whitworth et al. JCO PO, 2022.
9. Krop et al. SABCS 2020.
10. Zhao et al. JAMA Network Open, 2023.

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