# MammaPrint and BluePrint identify genomic differences in HR+ HER2- breast cancers from young Black and White women

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## Background

Hormone receptor positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer, the most common immunohistochemical subtype, remains the dominant contributor to annual breast cancer deaths worldwide across all racial and ethnic groups. Black women are 41% more likely to die from breast cancer compared to White women[1], predominantly among women diagnosed ≤ 50 years of age. Yet, Black women remain underrepresented in clinical trials and population-based studies. Thus, it is critical to better characterize tumor molecular features from young Black women to identify factors contributing to the existing racial survival disparity. In the current study, we compared risk of distant recurrence signature, MammaPrint (MP), molecular subtyping signature, BluePrint (BP), and whole transcriptome differences between young Black women with HR+ HER2- breast cancer compared to matched White controls.

## Methods

**Patients**: This study included 186 Black women aged ≤ 50 with stage I-III, HR+ HER2- breast cancer of whom, 98 were recruited from 2009-2014 as part of the BEST study (5R01CA204819-04) with follow-up data available (median 114.5 months). The remaining 88 Black women were enrolled in the ongoing FLEX Study (NCT03053193) from 2017. White women (n=186) were randomly selected from FLEX and matched by age, tumor stage, nodal status, and receptor status.

**Molecular Classification**: Tumors were classified through MammaPrint as Low Risk versus High Risk, with Low Risk further stratified into Ultra Low Risk and Low Risk (non-Ultra Low), and High Risk stratified into High Risk 1 and 2. High Risk 2 tumors exhibit superior chemosensitivity as demonstrated in a prior large clinical trial of breast cancer patients (ISPY2[2]). MammaPrint and BluePrint classified tumors as Luminal A-type (Low Risk), Luminal B-type (High Risk), HER2-type, or Basal-type.

**Whole Transcriptome Analysis**: Differential gene expression analysis was performed with R package 'limma' to compare Black and White women and further compare within each molecular subtype. Differentially expressed genes (DEGs) with a false discovery rate <0.05 were significant.

## Results

**Table 1. Clinical characteristics of patients**

| | Black Women (n = 186) | White Women ( n = 186) | p-value |
|---|---|---|---|
| Age, mean (sd) | 42.3 (5.77) | 42.3 (5.72) | 0.97 |
| T stage | | | |
| T1 | 95 (51.1%) | 98 (52.7%) | 0.84* |
| T2 | 76 (40.9%) | 78 (41.9%) | |
| T3 | 10 (5.4%) | 9 (4.8%) | |
| T4 | 3 (1.6%) | 1 (0.5%) | |
| TX | 2 (1.1%) | 0 | |
| N stage | | | |
| N0 | 98 (52.7%) | 97 (52.2%) | 0.83** |
| N+ | 82 (44.1%) | 85 (45.7%) | |
| N1 | 65 (79.3%) | 81 (95.3%) | |
| N2 | 12 (14.6%) | 3 (3.5%) | |
| N3 | 5 (6.1%) | 1 (1.2%) | |
| NX | 6 (3.2%) | 4 (2.2%) | |
| Grade | | | |
| G1 | 27 (14.5%) | 54 (29.0%) | <0.001* |
| G2 | 79 (42.5%) | 93 (50%) | |
| G3 | 69 (37.1%) | 38 (20.4%) | |
| GX | 11 (5.9%) | 1 (0.5%) | |

*not including unknown (TX, GX)
** N0 vs. N+

- Of 372 young women with localized, HR+ HER2- breast cancer, high grade tumors were significantly more frequent among Black compared to White women.
- Of patients with known germline mutation testing, 30% (14 of 46) of Black patients and 10% (9 of 90) of White patients had a pathogenic variant (data not shown).

**Figure 1. Frequency of MammaPrint risk category (A) and BluePrint molecular subtype (B) among Black and White women**

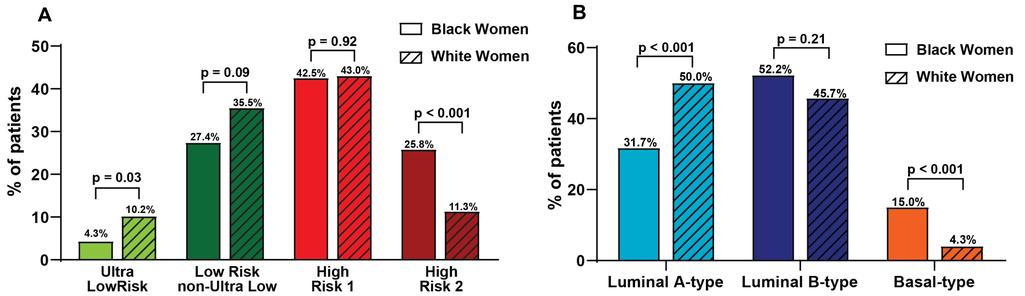
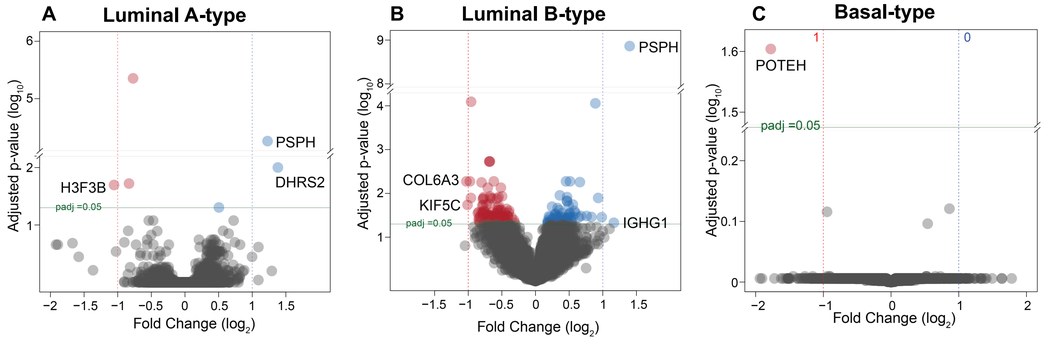



**Figure 2. Differential gene expression in breast cancer from Black women compared to White women in each molecular subtype**




- MammaPrint High Risk 2 tumors were significantly more frequent among Black compared to White women (**Figure 1A**).There were less Low Risk and significantly fewer Ultra Low Risk breast cancers in Black compared to White women (**Figure 1A**).
- There were more Luminal B-type tumors and significantly fewer Luminal A-type tumors in Black compared to White women (**Figure 1B**). Two HER2-type tumors were identified in Black patients (data not shown).
- BluePrint reclassified a significantly larger proportion of ER+ tumors as Basal-type in Black compared to White women (**Figure 1B**).
- Of 98 Black women with available survival data, the overall 5-year DMFS was 94.6% (95% CI, 87.6 – 97.7). A total of 9 Black patients had a death and/or distant recurrence event, 8 of whom had a High Risk tumor (6 Luminal B, 1 HER2, and 1 Basal) and 1 had a Low Risk Luminal A tumor (data not shown).
- Compared to White women, Black women with:
  - Luminal A-type tumors had 3 DEGs, one of which was the upregulation of suspected poor prognosis gene *PSPH* **(Figure 2A).**
  - Luminal B-type tumors had 192 DEGs with upregulation of poor prognosis genes, *PSPH* and *IGHG1* **(Figure 2B).**
  - Basal tumors had downregulation of *POTEH* **(Figure 2C).**

## Conclusion

Among young women with localized HR+ HER2- breast cancer, MammaPrint and BluePrint more robustly identified racial disparities in risk and subtype distribution beyond that identified through clinical factors adjusted for age and tumor characteristics. It is important to identify patients with ER+ tumors that reclassify as Basal-type, which occur at a higher frequency in Black compared to White women, as they have been reported to have worse outcomes compared to ER+, Luminal-type tumors. The transcriptomic differences among Black compared to White women across all BP subtypes provide novel insights about tumor biological differences. These findings have tremendous translational potential to identify etiologic underpinnings of racial survival disparities which may guide therapeutic strategies to improve outcomes.

**References**

1. Richardson et al. 2016. MMWR
2. Wlf et al. 2016. AACR

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