

# Genomically Basal-Type tumors demonstrate distinct immune profiles and chemosensitivity across self-reported race among patients enrolled in FLEX receiving neoadjuvant chemotherapy

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## Introduction

- BluePrint<sup>®</sup>, an 80-gene molecular subtyping signature, identifies intrinsic breast cancer (BC) biology beyond receptor-defined classifications.<sup>1</sup>
- Prior studies have shown higher frequencies of genomically Basal tumors among Black and Latin American patients (pts) compared to White pts.<sup>2,3</sup>
- However, limited data exist on chemotherapy response across race, and the biological basis of these differences remains unclear.
- Using whole transcriptome analysis (WTA) and clinical data from pts enrolled in the FLEX Study, we investigated racial differences in pathological complete response (pCR) and associated molecular features.
- The objective was to evaluate pCR rates and characterize underlying biological and immune profiles among pts with BluePrint Basal early BC treated with neoadjuvant chemotherapy (NCT).

## Methods

### Patient Population (n=451)

- Self-identified as Black, Latin American, or White with early BC enrolled in FLEX (NCT03053193) that had BluePrint Basal tumors, received NCT, with pCR data.

### Statistical Analysis

- Clinical characteristics were compared using chi-squared or Fisher's exact tests.
- Univariate and multivariate logistic regression models assessed the association between clinical variables and achieving pCR.

### Whole Transcriptome Analysis

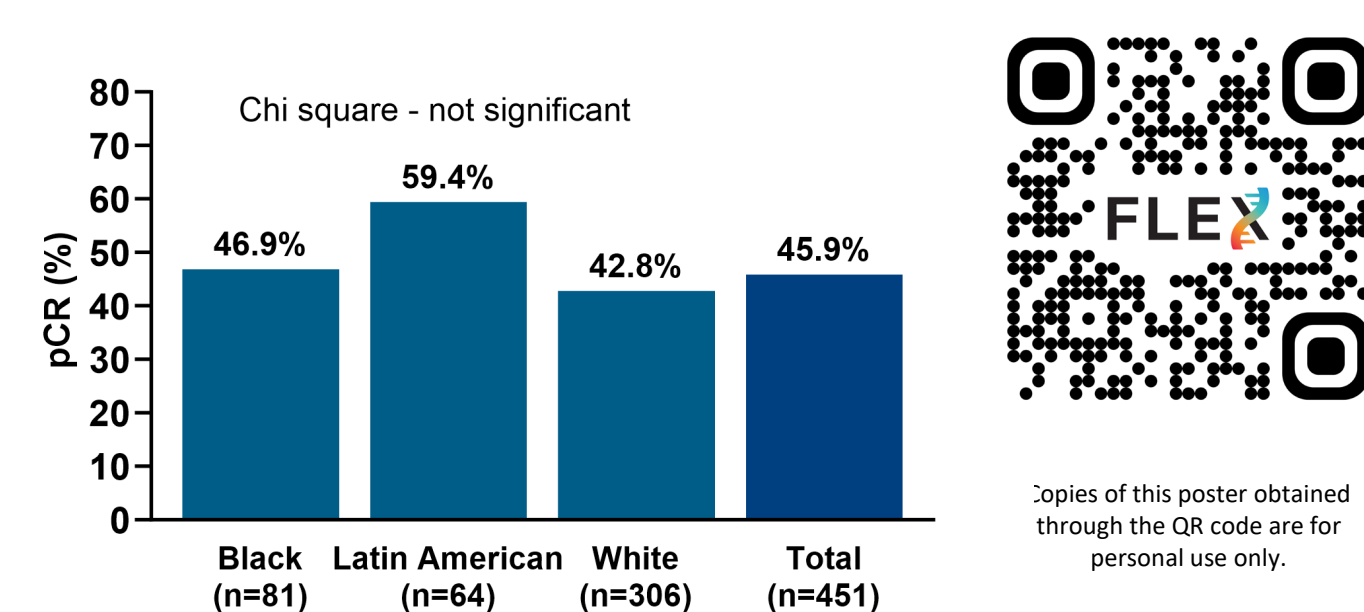
- Differentially expressed genes (DEGs) were evaluated using limma, and pathway enrichment was performed using gene set enrichment analysis (GSEA) with Hallmark gene sets between pts who achieved a pCR vs no pCR.
- Immune cell abundances were characterized using xCell.<sup>4</sup>
- Significance was defined as p < 0.05 for clinical variables and adjusted p < 0.05 for DEGs and xCell results.

**Table 1.** Clinical Characteristics of BluePrint Basal-Type Tumors

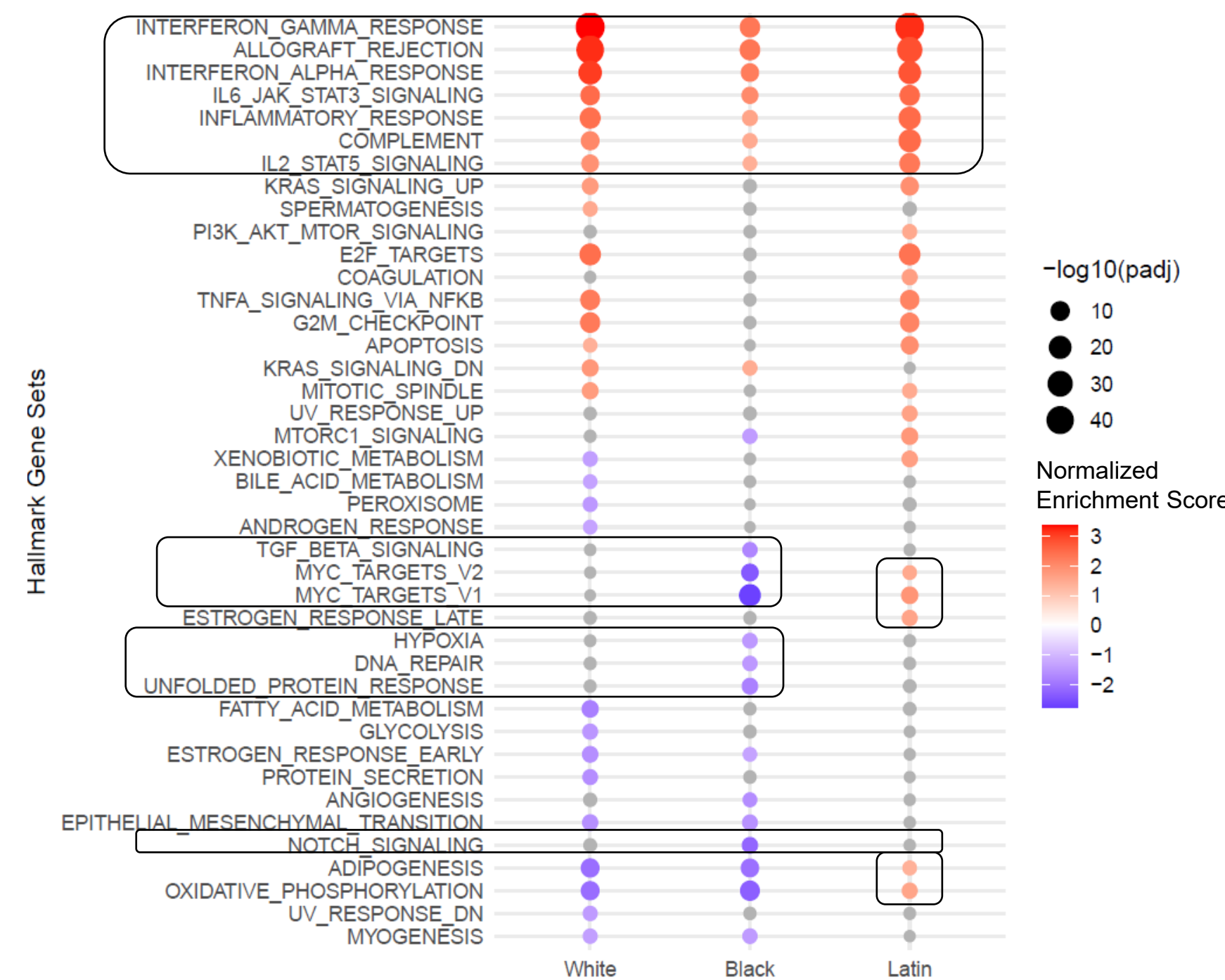
	Black (N=81)	Latin American (N=64)	White (N=306)	Total (N=451)	P-value
<b>Age</b>					< 0.001
Median	56	47.5	57	56	
Mean	55.19	49.48	56.55	55.29	
SD	12.39	12.23	13.59	13.39	
<b>Clin Subtype</b>					0.461
TNBC	46 (62.2%)	37 (63.8%)	192 (68.8%)	275 (66.9%)	
HR+HER2-	25 (33.8%)	16 (27.6%)	75 (26.9%)	116 (28.2%)	
HR-HER2+	3 (4.1%)	5 (8.6%)	12 (4.3%)	20 (4.9%)	
Unknown	7	6	27	40	
<b>Grade</b>					0.396
G1	0 (0.0%)	1 (1.7%)	2 (0.7%)	3 (0.7%)	
G2	15 (19.2%)	8 (13.3%)	37 (12.7%)	60 (14.0%)	
G3	63 (80.8%)	51 (85.0%)	252 (86.6%)	366 (85.3%)	
Unknown	3	4	15	22	
<b>T Size</b>					0.128
T1	18 (30.0%)	7 (16.7%)	62 (27.8%)	87 (26.8%)	
T2	33 (55.0%)	24 (57.1%)	128 (57.4%)	185 (56.9%)	
T3	9 (15.0%)	8 (19.0%)	21 (9.4%)	38 (11.7%)	
T4	0 (0.0%)	3 (7.1%)	12 (5.4%)	15 (4.6%)	
Unknown	21	22	83	126	
<b>LN Stage</b>					0.829
LN-	63 (85.1%)	52 (81.2%)	242 (82.3%)	357 (82.6%)	
LN+	11 (14.9%)	12 (18.8%)	52 (17.7%)	75 (17.4%)	
Unknown	7	0	12	19	
<b>MammaPrint</b>					0.033
High Risk 1	9 (11.1%)	1 (1.6%)	23 (7.5%)	33 (7.3%)	
High Risk 2	72 (88.9%)	62 (96.9%)	283 (92.5%)	417 (92.5%)	
Low Risk	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.2%)	
<b>NCT</b>					0.077
Chemo+Pltn	42 (51.9%)	40 (62.5%)	139 (45.4%)	221 (49.0%)	
AC-T	25 (30.9%)	19 (29.7%)	116 (37.9%)	160 (35.5%)	
TC	4 (4.9%)	1 (1.6%)	26 (8.5%)	31 (6.9%)	
Taxane	5 (6.2%)	1 (1.6%)	5 (1.6%)	11 (2.4%)	
Other	5 (6.2%)	3 (4.7%)	20 (6.5%)	28 (6.2%)	

Data presented as n (%); n, sample size; AAPI, Asian American and Pacific Islander; AIAN, American Indian or Alaska Native; ER, estrogen receptor; Pltn, Platinum; TC, taxanes; AC-T, anthracyclines and taxanes

**Figure 1.** Pathological Complete Response (pCR) to NCT by Race for BluePrint Basal-Type Tumors



**Figure 2.** Gene Set Enrichment Analysis (GSEA) among patients achieving pCR

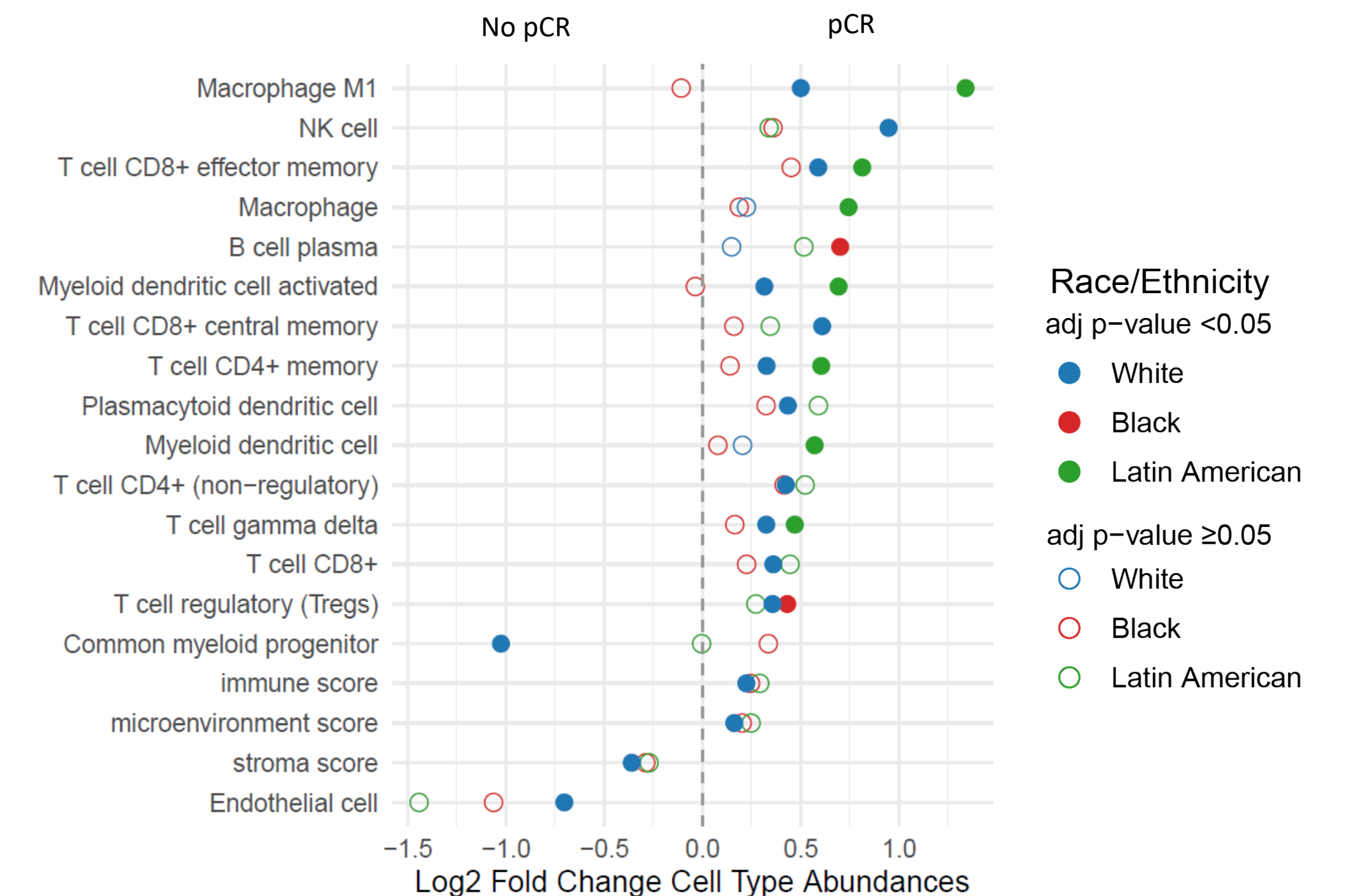


- Among all pts, GSEA for Hallmark gene sets revealed broad immune-related and inflammatory pathways in tumors of pts that achieved pCR across all races.
- MYC targets, estrogen response, adipogenesis, and oxidative phosphorylation pathways were significantly upregulated among Latin American pts and downregulated among Black pts compared to White pts achieving pCR.

**Table 2.** Multivariate logistic regression analysis for association of clinical factors and MammaPrint/BluePrint with pCR

Variable	Category	Univariate Odds Ratio (95% CI)	p-value	Multivariate Odds Ratio (95% CI)	p-value
MammaPrint Index	Continuous variable	0.12 (0.035–0.38)	<0.001	0.13 (0.036–0.44)	<b>0.0016</b>
Age	Continuous variable	0.98 (0.96–0.99)	<0.001	0.98 (0.97–1.00)	<b>0.048</b>
Self-reported Race	White	reference	-	-	-
	Black	1.18 (0.72–1.93)	0.51	1.15 (0.68–1.95)	0.61
	Latin American	1.95 (1.13–3.41)	0.017	1.53 (0.86–2.76)	0.15
Clinical Subtype	HR+HER2-	reference	-	-	-
	HR-HER2+	1.20 (0.50–2.80)	0.68	1.04 (0.40–2.65)	0.93
	TNBC	1.67 (1.09–2.57)	0.019	1.54 (0.97–2.46)	0.067
	Other/Unknown	1.00 (0.37–2.56)	0.99	0.95 (0.34–2.56)	0.92
	TC/Taxanes/Other	reference	-	-	-
NCT	AC-T	1.33 (0.73–2.46)	0.36	1.16 (0.61–2.22)	0.66
	Platinum containing	3.21 (1.83–5.81)	<0.001	2.76 (1.51–5.16)	<b>0.0012</b>

**Figure 3.** xCell Cell Type Enrichment among patients achieving pCR



- Immune xCell deconvolution revealed significant enrichment of:
  - Plasma B cells ( $\log_2FC = 0.70$ , adj. p = 0.048) and Treg cells ( $\log_2FC = 0.43$ , adj. p = 0.039) among Black pts.
  - In Latin American pts, pCR was associated with increases of M1 macrophages ( $\log_2FC = 1.34$ , adj. p = 0.039), T cells, macrophages, and myeloid dendritic cells.
  - White pts that did not achieve a pCR demonstrated significantly higher common myeloid progenitor cells ( $\log_2FC = -1.03$ , adj. p = 0.039), stroma, and endothelial cells.

## Conclusions

- BluePrint Basal-Type tumors demonstrate immune-active transcriptional profiles associated with NCT response across race, highlighting both shared and race-specific biological mechanisms of response.
- MammaPrint Index, age, and platinum-containing regimens remained significant variables associated with achieving pCR when accounting for clinical features, while race did not.
- Although self-reported race was not independently associated with pCR, the notably higher pCR rates observed among Latin American pts and the differences in WTA across racial groups highlight potential underlying biological or treatment response mechanisms that warrant further investigation in larger, racially diverse cohorts.
- Research in WTA differences is warranted between pts achieving pCR and no pCR across different age groups to further understand the interaction between tumor biology, immune activation, and age-related factors influencing NCT response.

## Results