ImPrint immune signature in 10,000 early-stage breast cancer patients from the real-world FLEX database

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Background

- Immune checkpoint inhibitors (**ICIs**) in combination with chemotherapy have demonstrated an improvement of pathologic complete response (pCR) in the I-SPY2 TRIAL[1-4].
- Not all patients benefit from immune checkpoint blockade and these new agents come with additional financial burden and may come with significant long-lasting side effects such as adrenal insufficiency. It is imperative to better understand who benefits most from ICIs.
- Response Predictive Subtypes (RPS) were developed in the I-SPY2 TRIAL using pre-treatment expression data from 987 MammaPrint High Risk patients, where 39% of HR+/HER2- tumors and 63% of TNBC (triple negative breast cancers) were identified as immune sensitive[1].
- In I-SPY2.2, RPS tumor classification uses ImPrint, a 53-gene signature that has been independently validated to predict the likelihood of a pCR with PD-1/PD-L1 ICIs with high sensitivity and specificity[5].

Objective

Using a real-world database of 10,000 patients enrolled in the FLEX trial, which includes patients who are largely underrepresented in most clinical trials, we identified patients with immune sensitivity (**ImPrint+**).

Methods

Patients: FLEX (NCT03053193) is an ongoing registry trial of patients with early-stage breast cancer who receive MammaPrint (**MP**) testing, with or without BluePrint (**BP**) molecular subtyping, and consent to clinically annotated full genome data collection.

Molecular Classification: MP is a 70-gene risk of distant metastasis signature that classifies patients as Low Risk or High Risk[6]. BP, an 80-gene molecular subtyping signature, categorizes patients' tumors as Luminal-, HER2- or Basal-Type[7].

Statistical analysis: Of those with available clinical data, differences in the distribution of ImPrint+ and ImPrint- results by clinical factors or genomics were assessed using a Chi-square test. A proportional z-test was used to assess differences in proportions.

Results

Table 1. Immune sensitivity across FLEX database

	ImPrint+	ImPrint-	Total	Significance
Age				
≤ 50 years	265 (14.4)	1572 (85.6)	1837 (22.7)	p < 0.001
> 50 years	480 (7.7)	5771 (92.3)	6251 (77.3)	
Menopausal status				
Pre-/peri-	217 (13.2)	1425 (86.8)	1642 (21.5)	p < 0.001
Post-	490 (8.2)	5506 (91.8)	5996 (78.5)	
Race/ethnicity				
AAPI	22 (11.3)	173 (88.7)	195 (2.5)	p < 0.001
Black/African American	141 (18.8)	609 (81.2)	750 (9.8)	
Latin-X	54 (16.2)	280 (83.8)	334 (4.3)	
White	477 (7.5)	5897 (92.5)	6374 (82.9)	
Other	2 (5.4)	35 (94.6)	37 (0.5)	
Tumor stage, cT				
cT0/Tis	0	7 (100)	7 (0.1)	p < 0.001
cT1	281 (6.6)	3979 (93.4)	4260 (64.0)	
cT2	256 (12.6)	1775 (87.4)	2031 (30.5)	
cT3	48 (16.7)	240 (83.3)	288 (4.3)	
cT4	13 (19.4)	54 (80.6)	67 (1.0)	
Nodal stage, cN				
cN0	409 (8.3)	4496 (91.7)	4905 (77.3)	p < 0.001
cN1	138 (10.6)	1161 (89.4)	1299 (20.5)	
cN2	23 (23.7)	74 (76.3)	97 (1.5)	
cN3	11 (25.6)	32 (74.4)	43 (0.7)	
Clinical subtype				
HR+/HER2-	321 (5.0)	6079 (95.0)	6400 (86.6)	p < 0.001
HR+/HER2+	54 (12.7)	373 (87.3)	427 (5.8)	
HR-/HER2+	50 (38.8)	79 (61.2)	129 (1.8)	
TNBC	257 (59.4)	176 (40.6)	433 (5.9)	
MammaPrint				
Low Risk	12 (0.3)	4508 (99.7)	4520 (48.8)	p < 0.001
High Risk	840 (17.7)	3908 (82.3)	4748 (51.2)	
BluePrint				
Luminal-Type	191 (2.5)	7507 (97.5)	8771 (86.8)	p < 0.001
HER2-Type	75 (21.1)	280 (78.9)	377 (4.0)	
Basal-Type	564 (69.5)	248 (30.5)	873 (9.2)	

Results represented as n (%)
AAPI, Asian American Pacific Islander; **AA**, African American; **LA**, Latin American

Figure 1. Classification of clinical subtypes (left) by genomic MP risk (middle) and immune sensitivity (right). MammaPrint is categorized as Low Risk (**Low**) or High Risk (**High**).

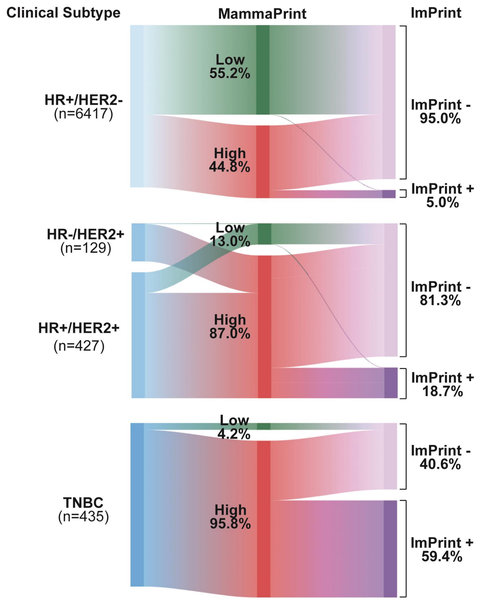
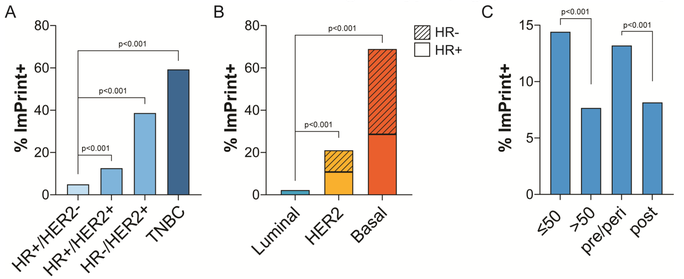
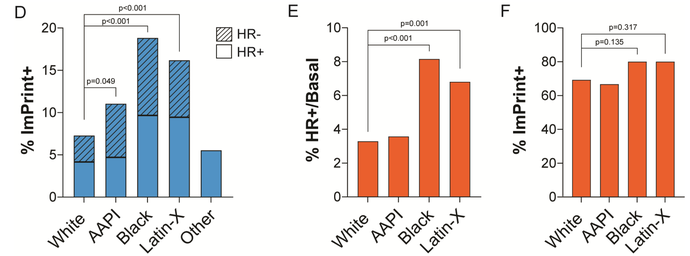


Figure 2. ImPrint+ tumors identified among subtypes, age, and race/ethnicity



Patients with a higher likelihood of being ImPrint+ were **(A)** clinically defined as HER2+ and TNBC, **(B)** patients with BP HER2-Type and Basal-Type, and **(C)** younger or pre/peri-menopausal patients.



(D) Patients of Black or Latin-X race/ethnicity had a higher proportion of ImPrint + tumors than White patients. **(E)** Black and Latin-X patients had a greater frequency of HR+, BP Basal-Type tumors than White patients. **(F)** Among patients with HR+/Basal tumors, there were no significant differences in the proportion of immune sensitivity by race/ethnicity.

Conclusions

- ❖ In this study, most patients who are predicted to benefit from ICIs have MP High Risk or BP Basal-Type tumors.
- ❖ 321 (5.0%) patients with HR+/HER2- tumors were ImPrint+.
- ❖ Similar frequencies of immune sensitivity were observed in FLEX as in I-SPY2[1-3] when comparing MP High Risk patients with clinically high risk characteristics.
- ❖ Younger women and patients of Black or Latin race/ethnicity who more often have more aggressive tumors[8,9] also have higher proportions of ImPrint+ tumors.
- ❖ This large, real-world dataset enables the identification of populations who may benefit from immune therapy beyond those typically included in clinical trials and supports the testing of checkpoint inhibitors in the immune-positive subtype.
- ❖ Here, we utilized FLEX to evaluate a clinically relevant genomic signature, which may be further optimized in the future by subtype and used to inform treatment decisions.
- ❖ This first look at immune sensitivity with ImPrint in the 10,000 patient FLEX database generates preliminary data and hypotheses that will be explored in future FLEX substudies, and this analysis was only possible using the FLEX full genome data.

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