Association of the 70-gene assay and homologous recombination deficiency in patients with High Risk 2 breast cancers

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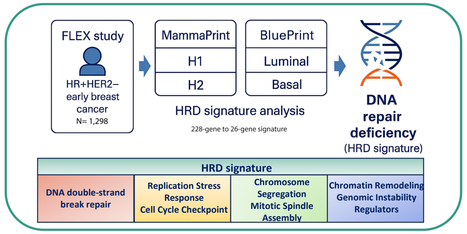
Background

- Homologous recombination deficiency (HRD) is a biomarker for impaired DNA repair, genomic instability and sensitivity to DNA-damaging agents[1].
- MammaPrint® (MP) is a 70-gene assay that stratifies early breast cancer (EBC) by recurrence risk[2].
- MammaPrint risk groups include UltraLow Risk (UL), Low Risk (LR), High Risk 1 (H1) and High Risk 2 (H2).
- Patients with H2 tumors derive greater benefit from anthracycline-based chemotherapy than patients with H1 cancers.
- This study analyzes HRD signatures to assess whether MammaPrint gene expression profiling may capture DNA repair deficiency in tumors with distinct risk of recurrence.

Methods

- Patients enrolled in the ongoing prospective, observational FLEX Study (NCT03053193), with HR+HER2- EBC, who consented to full transcriptome and clinical data collection, with available MammaPrint and BluePrint® (BP; Luminal or Basal) results (N=1298) were included in this study (Figure 1).
- HRD status assessed using a 228-gene signature was further refined into a 26-gene panel as described by Jacobson et al, 2023[3].
- Gene expression data were processed using Limma R package, with median probe expression per gene.
- HRD scores were compared across MammaPrint and BluePrint groups using t-tests.

Figure 1. HRD Study design.



Results

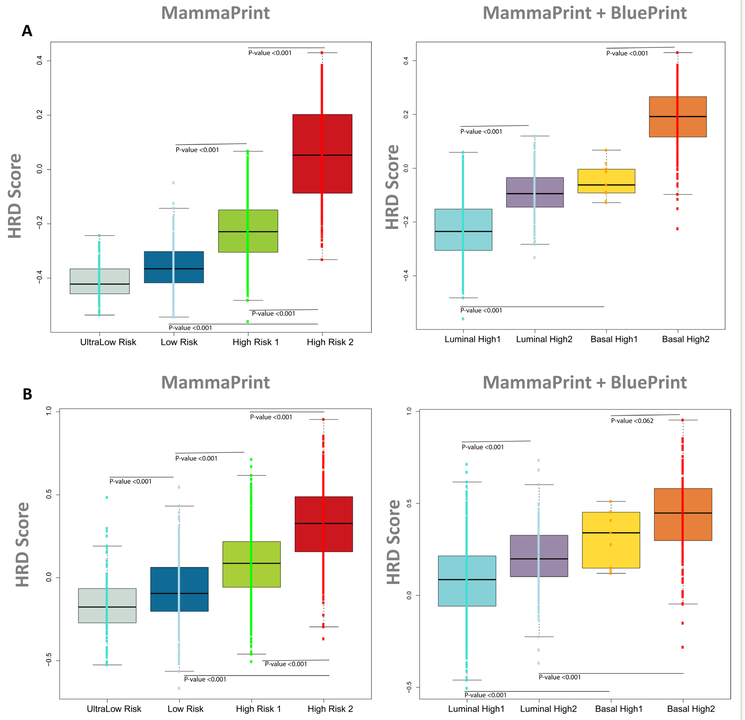
Table 1. Clinical Characteristics

		MammaPrint Risk Group				
		UltraLow	Low	High 1	High 2	P-value
BluePrint Subtype	Basal	0 (0.0%)	0 (0.0%)	9 (5.1%)	168 (94.9%)	<0.001
	Luminal	95 (8.5%)	286 (25.5%)	612 (54.6%)	128 (11.4%)	
Sex	Female	94 (7.3%)	283 (22.1%)	610 (47.5%)	296 (23.1%)	0.115
	Male	1 (6.7%)	3 (20.0%)	11 (73.3%)	0 (0.0%)	
Age	Mean	60 (±10)	60 (±12)	56 (±13)	52 (±13)	>0.001
Race	AAPI	1 (2.9%)	7 (20.6%)	17 (50.0%)	9 (26.5%)	0.002
	Black	11 (6.5%)	21 (12.4%)	85 (50.3%)	52 (30.8%)	
	Latin American/Hispanic	5 (4.0%)	26 (20.9%)	52 (41.9%)	41 (33.0%)	
	NA	6 (7.2%)	18 (21.7%)	36 (43.4%)	23 (27.7%)	
	Other	0 (0.0%)	5 (33.3%)	9 (60.0%)	1 (6.7%)	
	White	72 (8.2%)	209 (23.9%)	422 (48.3%)	170 (19.5%)	
Menopausal.Status	Pre-/Peri-	13 (3.4%)	65 (17.1%)	194 (50.9%)	109 (28.6%)	<0.001
	Post-	72 (8.7%)	210 (25.5%)	380 (46.1%)	163 (19.8%)	
	NA	0 (0.0%)	5 (33.3%)	7 (46.7%)	3 (20.0%)	
	Unknown	6 (15.0%)	5 (12.5%)	20 (50.0%)	9 (22.5%)	
Tumor Stage	T1	36 (12.5%)	72 (24.9%)	125 (43.3%)	56 (19.4%)	<0.001
	T2	16 (3.6%)	67 (15.2%)	234 (53.2%)	123 (28.0%)	
	T3	4 (3.1%)	32 (24.4%)	69 (52.7%)	26 (19.8%)	
	T4	3 (5.5%)	10 (18.2%)	25 (45.5%)	17 (30.9%)	
	NA	36 (9.4%)	105 (27.4%)	168 (43.9%)	74 (19.3%)	
Nodal Stage	N0	39 (8.1%)	115 (24.0%)	206 (42.9%)	120 (25.0%)	0.002
	N1	13 (3.6%)	55 (15.2%)	212 (58.6%)	82 (22.7%)	
	N2	1 (3.7%)	3 (11.1%)	14 (51.9%)	9 (33.3%)	
	N3	0 (0.0%)	1 (6.7%)	8 (53.3%)	6 (40.0%)	
	NA	38 (9.8%)	107 (27.6%)	169 (43.6%)	74 (19.1%)	
	Unknown	4 (15.4%)	5 (19.2%)	12 (46.2%)	5 (19.2%)	
Nodal Status	LN-	39 (8.1%)	115 (24.0%)	206 (42.9%)	120 (25.0%)	<0.001
	LN+	14 (3.5%)	59 (14.6%)	234 (57.9%)	97 (24.0%)	
	NA	38 (9.8%)	107 (27.6%)	169 (43.6%)	74 (19.1%)	
	Unknown	4 (15.4%)	5 (19.2%)	12 (46.2%)	5 (19.2%)	
Grade	G1	45 (24.7%)	83 (45.6%)	53 (29.1%)	1 (0.5%)	<0.001
	G2	47 (7.6%)	169 (27.4%)	351 (56.9%)	50 (8.1%)	
	G3	0 (0.0%)	12 (2.9%)	175 (42.2%)	228 (54.9%)	
	NA	1 (2.9%)	8 (22.9%)	19 (54.3%)	7 (20.0%)	
	Unknown	2 (4.1%)	14 (28.6%)	23 (46.9%)	10 (20.4%)	

Data presented as n (%); Non available (NA) / Unknown were included in the table but excluded from the analysis; AAPI, Asian American and Pacific Islander; All patients in this cohort were treated with neoadjuvant chemotherapy. Luminal A and Luminal B were combined in this analysis.

- In this FLEX cohort, the majority of tumors were classified as MammaPrint High Risk 1 Luminal;
- Patients were predominantly female with the majority being post-menopausal;
- Most patients had no nodal involvement and Grade 2 tumors (Table 1).

Figure 2. HRD score across MammaPrint groups and BluePrint subtyping based on (A) HRD 228-gene signature and (B) HRD 26-gene signature



Results

- In HR+HER2- EBC, HRD scores differed significantly by both MammaPrint risk groups and BluePrint subtypes.
- Using the 228-gene HRD signature, MP H2 tumors showed higher HRD scores than H1 tumors (p<0.001; Figure 2A).
- Within Luminal type tumors, H2 demonstrated higher HRD scores than H1 (p<0.001; Figure 2A).
- Basal tumors exhibited higher HRD scores than Luminal tumors within both MP H1 and H2 groups (p<0.001); H2 Basal tumors had higher HRD than H1 Basal (p<0.001; Figure 2A).
- Similar patterns were observed using the 26-gene HRD panel, with higher HRD in H2 vs H1 and in Basal vs Luminal tumors; H2 Basal showed higher scores but did not reach statistical significance (p=0.062; Figure 2B).

Conclusions

- MammaPrint and BluePrint identified distinct differences in underlying HRD biology, with H2 Basal tumors enriched for HRD and H1 Luminal tumors demonstrating relative homologous recombination proficiency.
- These biological differences may explain the observed anthracycline chemotherapy and immunotherapy benefit in patients with H2 tumors.
- Findings provide further evidence supporting MammaPrint as a tool for refined therapy selection in genomically high-risk disease.
- Additional research is warranted to evaluate MammaPrint and BluePrint as surrogate markers for HRD-sensitive therapies (e.g., PARP inhibitors, carboplatin).

Acknowledgement

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References

[1]Doig et al., Mod Pathol. 2023 [2]Cardoso et al., N Engl J Med. 2016 [3]Jacobson et al., Genome Medicine. 2023