70-Gene Signature High Risk Classification Provides Stronger Prognostic Value Than Histologic Grade in HR+HER2– Early Breast Cancer

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Background

- Pivotal trials of immunotherapy and CDK4/6 inhibitors in early-stage hormone-receptor positive (HR+) HER2 negative (HER2–) breast cancer have relied on histologic grade 3 to define high-risk disease[1].
  - Studies have shown that histological grade presents variability and limited prognostic accuracy [2,3].
- The 70-gene MammaPrint® (MP) signature provides a genomic recurrence risk assessment[4] and predicts chemotherapy[5,6] (CT) and endocrine therapy[7,8] benefit.
- We evaluated the 5-year distant relapse-free survival (DRFS) among CT-treated patients with HR+HER2–, MP High Risk 1 (H1) vs High Risk 2 (H2) breast cancer.
- Prognostic performance of MP H1 and H2 was also compared to clinicopathologic variables such as histologic grade.

Methods

Study Cohort

- Patients included in this analysis were enrolled in the FLEX Study (NCT03053193)
- Eligible patients had HR+HER2-, MammaPrint High Risk breast cancer, who received CT and had follow-up data available (n=1407).

MammaPrint High Risk Stratification

MammaPrint	High Risk 1 (H1) (N=1043)	High Risk 2 (H2) (N=364)

Statistics

- Kaplan–Meier (KM) survival analyses were performed, with median follow-up of 3.2 yrs.
- DRFS was the primary endpoint per STEEP 2.0[9].
- Cox proportional hazards models assessed how grade (G), tumor (T) size, lymph node (LN), and menopausal status compared to MP risk stratification.
- P-values of less than 0.05 were considered significant.

Table 1. Clinical Characteristics of FLEX patients with HR+HER2- disease treated with chemotherapy

	High1 (N=1043)	High2 (N=364)	Overall (N=1407)	P-value
BP Subtype				
Luminal B	1028 (98.6%)	189 (51.9%)	1217 (86.5%)	<0.001
Basal	15 (1.4%)	175 (48.1%)	190 (13.5%)	
Age (Years)				
Mean (SD)	58 (± 12)	55 (± 13)	57 (± 12)	0.00428
Menopausal Status				
Pre-/Peri-	256 (24.5%)	104 (28.6%)	360 (25.6%)	0.569
Post-	712 (68.3%)	240 (65.9%)	952 (67.7%)	
Unknown	75 (7.2%)	20 (5.5%)	95 (6.8%)	
Race				
AAPI	34 (3.3%)	12 (3.3%)	46 (3.3%)	0.236
American Indian or Alaska Native	2 (0.2%)	1 (0.3%)	3 (0.2%)	
Black	115 (11.0%)	64 (17.6%)	179 (12.7%)	
Latin American/Hispanic	60 (5.8%)	23 (6.3%)	83 (5.9%)	
Multiple	5 (0.5%)	0 (0%)	5 (0.4%)	
White	756 (72.5%)	233 (64.0%)	989 (70.3%)	
Unknown	71 (6.8%)	31 (8.5%)	102 (7.2%)	
Tumor Size				
T1	618 (59.3%)	174 (47.8%)	792 (56.3%)	0.017
T2	362 (34.7%)	153 (42.0%)	515 (36.6%)	
T3	37 (3.5%)	19 (5.2%)	56 (4.0%)	
T4	12 (1.2%)	5 (1.4%)	17 (1.2%)	
Unknown	14 (1.3%)	13 (3.6%)	27 (1.9%)	
Lymph Node Status				
LN-	721 (69.1%)	265 (72.8%)	986 (70.1%)	0.792
LN+	294 (28.2%)	91 (25.0%)	385 (27.4%)	
Unknown	28 (2.7%)	8 (2.2%)	36 (2.6%)	
Grade				
G1	138 (13.2%)	7 (1.9%)	145 (10.3%)	<0.001
G2	642 (61.6%)	86 (23.6%)	728 (51.7%)	
G3	256 (24.5%)	270 (74.2%)	526 (37.4%)	
Unknown	7 (0.7%)	1 (0.3%)	8 (0.6%)	
Chemotherapy				
Neoadjuvant therapy	185 (17.7%)	145 (39.8%)	330 (23.5%)	<0.001
Adjuvant therapy	846 (81.1%)	217 (59.6%)	1063 (75.6%)	
Non-surgical	12 (1.2%)	2 (0.5%)	14 (1.0%)	
Chemo Regimen				
TC	605 (58.0%)	144 (39.6%)	749 (53.2%)	<0.001
AC-T	300 (28.8%)	162 (44.5%)	462 (32.8%)	
Chemo+Platinum	23 (2.2%)	19 (5.2%)	42 (3.0%)	
Other	91 (8.7%)	30 (8.2%)	121 (8.6%)	
Unknown	24 (2.3%)	9 (2.5%)	33 (2.3%)	
ER Staining (%)				
1-10%	14 (1.3%)	63 (17.3%)	77 (5.5%)	<0.001
>10%	1019 (97.7%)	273 (75.0%)	1292 (91.8%)	
Unknown	10 (1.0%)	28 (7.7%)	38 (2.7%)	

Data presents n (%) unless indicated otherwise. p<0.05 indicates significance. Abbreviations: AAPI, Asian American and Pacific Islander; LN, lymph node; G, Grade; TC, taxanes; AC-T, anthracycline-taxane; ER, Estrogen Receptor.

Figure 1. Kaplan-Meier Curve of Distant Relapse-Free Survival (DRFS) of Patients with MammaPrint High Risk Disease

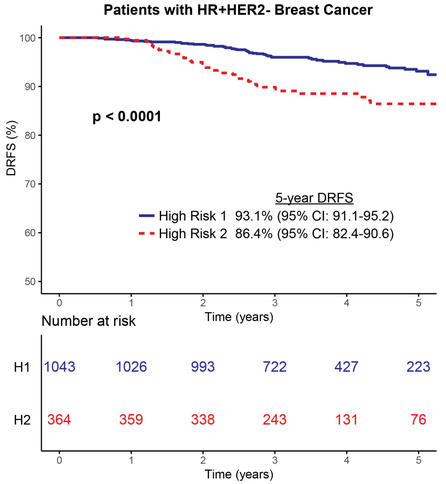

Figure 2. Kaplan-Meier Curve of Distant Relapse-Free Survival (DRFS) of Patients with Grade 3 tumors and MammaPrint High Risk Disease

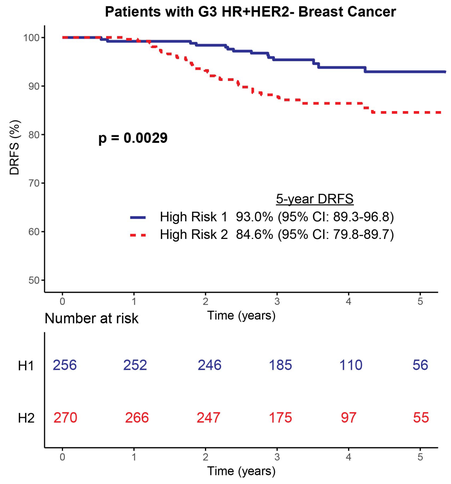

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Table 2. Cox proportional hazards – Univariate and Multivariate analysis

Variables		HR (univariable)	HR (multivariable)
MP Group	High1	ref	ref
	High2	**2.37 (1.58-3.55, p<0.001)**	**2.14 (1.26-3.63, p=0.005)**
Menopausal Status	Post-	ref	ref
	Pre-/Peri-	0.86 (0.53-1.38, p=0.525)	0.71 (0.43-1.16, p=0.171)
Tumor Size	T1/2	ref	ref
	T3/4	**4.22 (2.46-7.22, p<0.001)**	**3.41 (1.89-6.16, p<0.001)**
Lymph Node Status	LN-	ref	ref
	LN+	**2.15 (1.42-3.24, p<0.001)**	**1.84 (1.18-2.89, p=0.007)**
Grade	Non G3	ref	ref
	G3	**1.95 (1.30-2.92, p=0.001)**	1.24 (0.75-2.04, p=0.398)

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Results

- Of 1407 patients with HR+HER2- EBC treated with neo/adjuvant CT, 74% had H1 and 26% H2 breast cancer
  - Patients with H2 breast cancer were younger (p=0.004), more often G3, and had larger tumors, while LN and menopausal status were similar to patients with H1 breast cancer (Table 1).
- Patients with H2 breast cancer had worse DRFS at 5 yrs (86.4, 95% CI 82.4–90.6) vs H1 (93.1, 95% CI 91.1–95.2), an absolute difference of 6.7% (p<0.001) (Figure 1).
- When stratifying patients with G3 cancer by MP High Risk, H2 remained significantly associated with worse outcomes (8.4% absolute difference at 5 yrs, p=0.0029) (Figure 2).
- Multivariate Cox analyses confirmed higher recurrence risk for H2 vs H1 (uni: HR 2.37, p<0.001; multi: HR 2.14, p=0.005) (Table 2).
  - T size and LN were significantly associated with DRFS event, while grade lost significance after adjustment.

Conclusions

- Among patients with HR+HER2– breast cancer treated with CT, MP H2 was associated with significantly worse DRFS compared to H1 after adjusting for clinicopathologic factors and receipt of chemotherapy.
- Histological grade lost independent prognostic value when corrected for MP status, indicating that MP provides more accurate prognostic information.
- Prior data suggest anthracycline-based CT improves outcomes in patients with MP H2 breast cancer[10]. Additionally, H2 tumors were shown to have an immune active state[11], share many features of TNBC[12], therefore, may have substantial risk of recurrence with current therapies.
- Data from I SPY2 suggest MP H2 breast cancer benefits from neoadjuvant immunotherapy[13,14] which is now under investigation under the nationwide prospective randomized trial SWOG 2206 (NCT06058377).

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