

70-Gene Signature Provides Prognostic Value Beyond Ki67 in HR+HER2– Early Breast Cancer (EBC)

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Background

- Ki67 is commonly used to inform chemotherapy decision-making in patients with HR+/HER2- early breast cancer (EBC).

- Clinical utility of Ki67 is limited by inter-observer variability, scoring inconsistencies and lack of consensus for optimal cutoffs¹.

- Genomic assays like the 70-gene MammaPrint (MP) assay provide validated prognostic and predictive risk stratification to support treatment decisions².

- MammaPrint ® is used to guide therapy decisions by identifying patients at UltraLow (UL), Low Risk (LR) and High Risk (H1 and H2) of recurrence.

- Emerging data demonstrate a strong association between MammaPrint risk classification and endocrine response, highlighting the potential of genomic profiling to provide clinically relevant prognostic information beyond Ki67 and further refine treatment decision-making³.

- This real-world study evaluated the prognostic performance of MammaPrint in tumors with baseline Ki67 ≥ 20%, a population generally associated with higher proliferative activity and increased recurrence risk.

Methods

- This study included 4,261 participants with HR+HER2- EBC enrolled in FLEX (NCT03053193) with MammaPrint results and available follow up.

- Distant Recurrence-free survival (DRFS) was evaluated among tumors with Ki67 ≥ 20% stratified by MammaPrint UltraLow + Low Risk (UL+LR), High Risk 1 (H1), or High Risk 2 (H2).

- Survival analyses were performed (3.2 yrs median follow up).

- Cox proportional hazards models assessed associations between MammaPrint, clinical features, and DRFS.

Results

Table 1. Clinical Characteristics

Clinical Characteristics by MP within >=20% Ki67 patients				
	LOW RISK (N=648)	HIGH RISK (N=1239)	Overall (N=1887)	P-value
MP Group				
UltraLow	99 (15.3%)	0 (0%)	99 (5.2%)	<0.001
Low	549 (84.7%)	0 (0%)	549 (29.1%)	
High1	0 (0%)	967 (78.0%)	967 (51.2%)	
High2	0 (0%)	272 (22.0%)	272 (14.4%)	
BP Subtype				
Luminal A	616 (95.1%)	0 (0%)	616 (32.6%)	<0.001
Luminal B	0 (0%)	1087 (87.7%)	1087 (57.6%)	
Basal	0 (0%)	93 (7.5%)	93 (4.9%)	
HER2	0 (0%)	3 (0.2%)	3 (0.2%)	
Not requested	32 (4.9%)	56 (4.5%)	88 (4.7%)	
Age (Years)				
Mean (SD)	61 (± 11)	59 (± 13)	60 (± 12)	0.0111
Menopausal Status				
Pre-/Peri-	128 (19.8%)	281 (22.7%)	409 (21.7%)	0.689
Post-	478 (73.8%)	883 (71.3%)	1361 (72.1%)	
Unknown	42 (6.5%)	75 (6.1%)	117 (6.2%)	
Race				
White	499 (77.0%)	877 (70.9%)	1376 (73.0%)	0.041
Black	44 (6.8%)	144 (11.6%)	188 (10.0%)	
Latin American/Hispanic	51 (7.9%)	90 (7.3%)	141 (7.5%)	
AAPI	9 (1.4%)	36 (2.9%)	45 (2.4%)	
Multiple	3 (0.5%)	2 (0.2%)	5 (0.3%)	
Unknown	42 (6.5%)	88 (7.1%)	130 (6.9%)	
Tumor Size				
T1	426 (65.7%)	762 (61.5%)	1188 (63.0%)	0.178
T2	222 (34.3%)	477 (38.5%)	699 (37.0%)	
Lymph Node Stage				
N0	454 (70.1%)	844 (68.1%)	1298 (68.8%)	0.682
N1	194 (29.9%)	395 (31.9%)	589 (31.2%)	
Grade				
G1	153 (23.6%)	78 (6.3%)	231 (12.2%)	<0.001
G2	403 (62.2%)	615 (49.6%)	1018 (53.9%)	
G3	91 (14.0%)	537 (43.3%)	628 (33.3%)	
Unknown	1 (0.2%)	9 (0.7%)	10 (0.5%)	
Histologic Tumor Type				
IDC	511 (78.9%)	1101 (88.9%)	1612 (85.4%)	<0.001
ILC	93 (14.4%)	75 (6.1%)	168 (8.9%)	
Mixed	37 (5.7%)	37 (3.0%)	74 (3.9%)	
Other	7 (1.1%)	17 (1.4%)	24 (1.3%)	
Unknown	0 (0%)	9 (0.7%)	9 (0.5%)	
Systemic Therapies				
ET only	597 (92.1%)	317 (25.6%)	914 (48.4%)	<0.001
ET+CT	51 (7.9%)	922 (74.4%)	973 (51.6%)	

Data presented as n (%); Unknown values were excluded from the analysis; n, sample size; AAPI, Asian American and Pacific Islander; ER, estrogen receptor; IDC, Invasive Ductal Carcinoma; ILC, Invasive Lobular Carcinoma; ET, Endocrine Therapy; CT, Chemotherapy.

Figure 1. Distribution of MammaPrint subgroups across Ki67 categories (N=4,261)

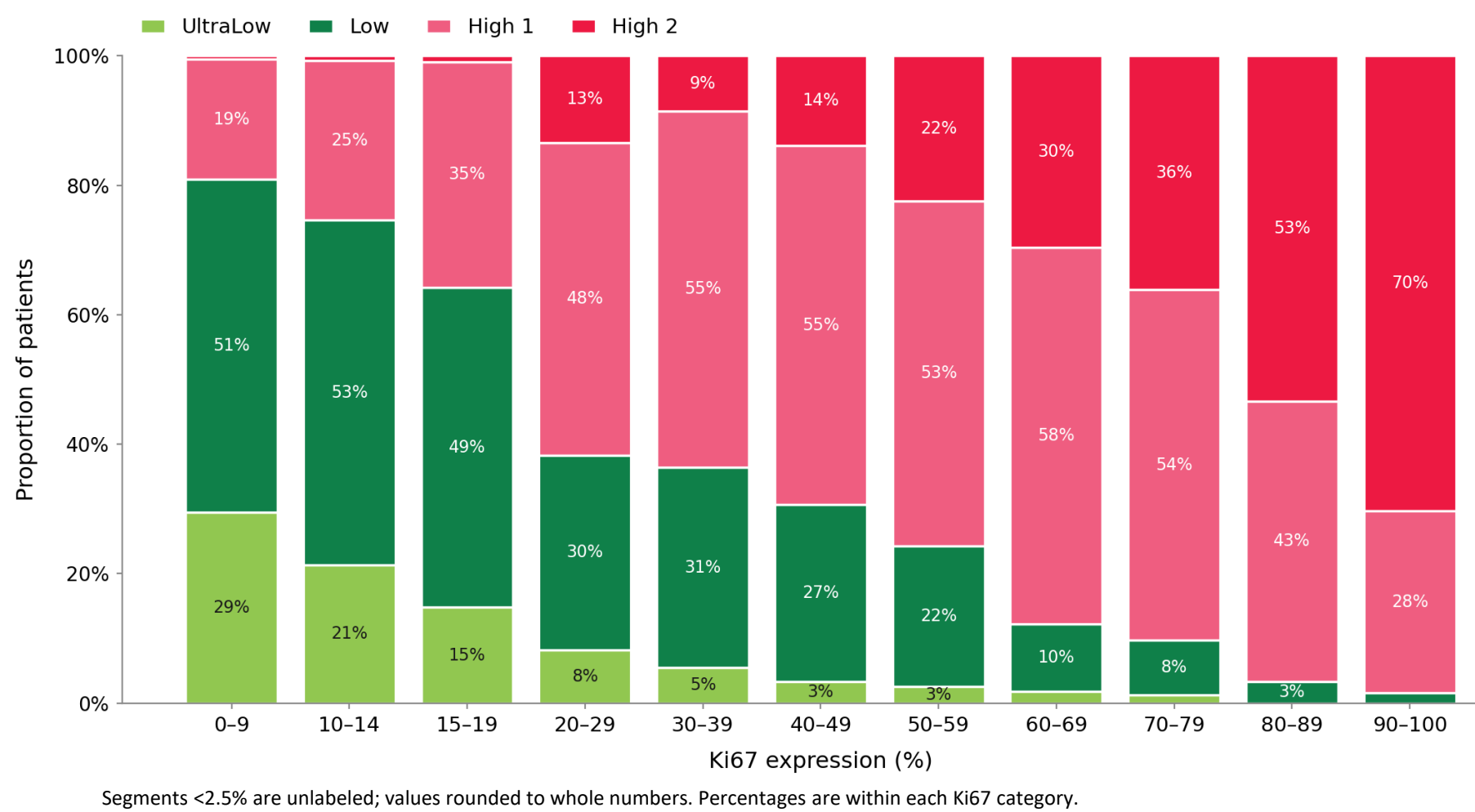
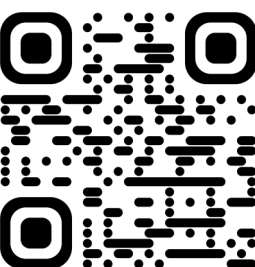


Table 2: Univariate and Multivariate Cox proportional hazards in overall population and in Ki67≥20%

Variable	Overall population		Ki67 ≥20%	
	Univariable	Multivariable	Univariable	Multivariable
MP group ref: LR				
High 1	1.42 (1.04-1.93)	0.029	1.34 (0.90-2.01)	0.148
High 2	2.52 (1.61-3.93)	<0.001	2.46 (1.32-4.59)	0.005
Age (per year) ref: Post-				
Pre-/Peri-	1.04 (1.03-1.06)	<0.001	1.05 (1.03-1.07)	<0.001
Menopausal status ref: Post-				
Pre-/Peri-	0.50 (0.31-0.78)	0.003	1.33 (0.75-2.38)	0.329
Tumor size ref: T1				
T2	1.76 (1.32-2.36)	<0.001	1.42 (1.03-1.95)	0.033
LN stage ref: N0				
N1	1.87 (1.39-2.52)	<0.001	1.78 (1.29-2.46)	<0.001
Grade ref: G1				
G2	1.24 (0.85-1.80)	0.261	1.00 (0.67-1.49)	0.998
G3	2.07 (1.37-3.14)	0.001	1.49 (0.87-2.53)	0.145
Systemic therapy ref: ET only				
ET+CT	1.08 (0.79-1.46)	0.634	0.74 (0.49-1.12)	0.158
Ki67 ref: <20%				
≥20%	1.44 (1.08-1.93)	0.014	1.09 (0.63-1.89)	0.575

Cox proportional hazards. Bold: p<0.05. In Ki67>20%, MP reference is UL+LR and grade is G3 vs. non G3. -: not included in the model.



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Figure 2. 3-year DRFS by MammaPrint within Ki67≥20% Patients – Low Risk vs High Risk

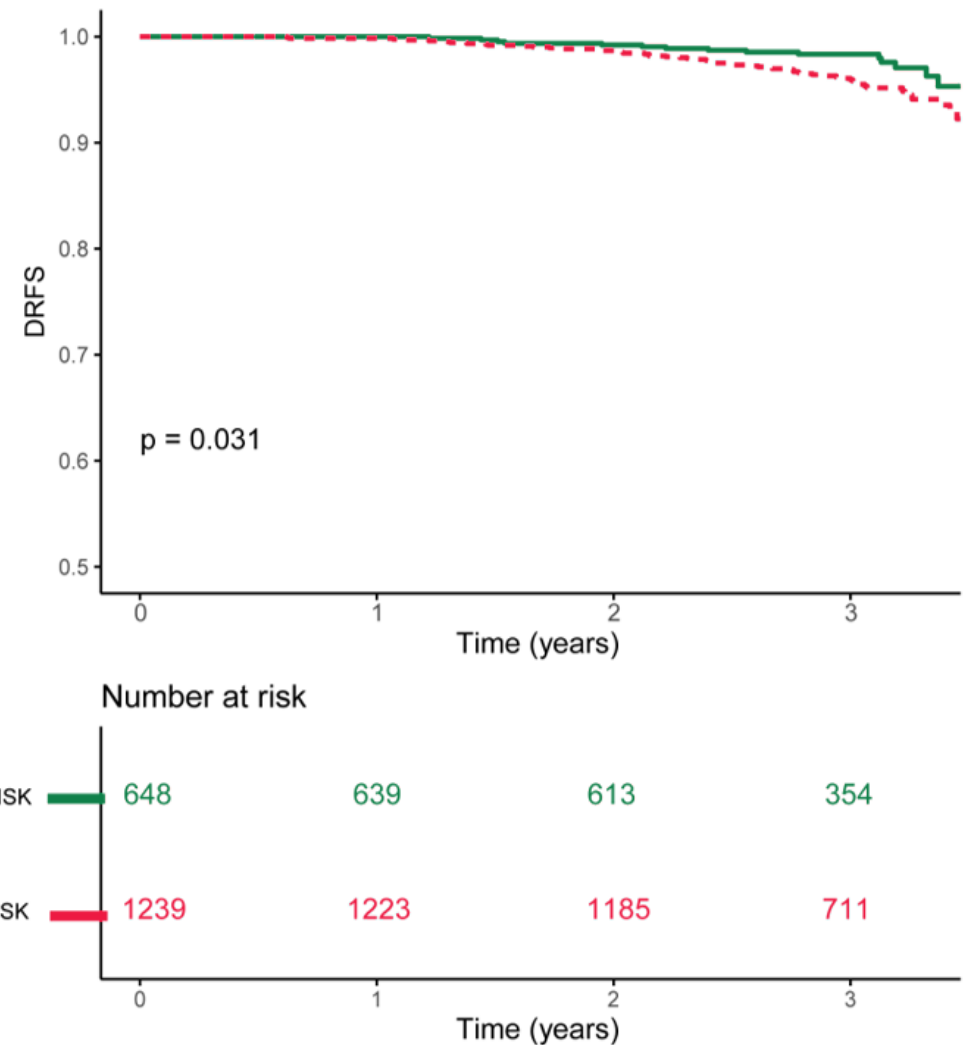
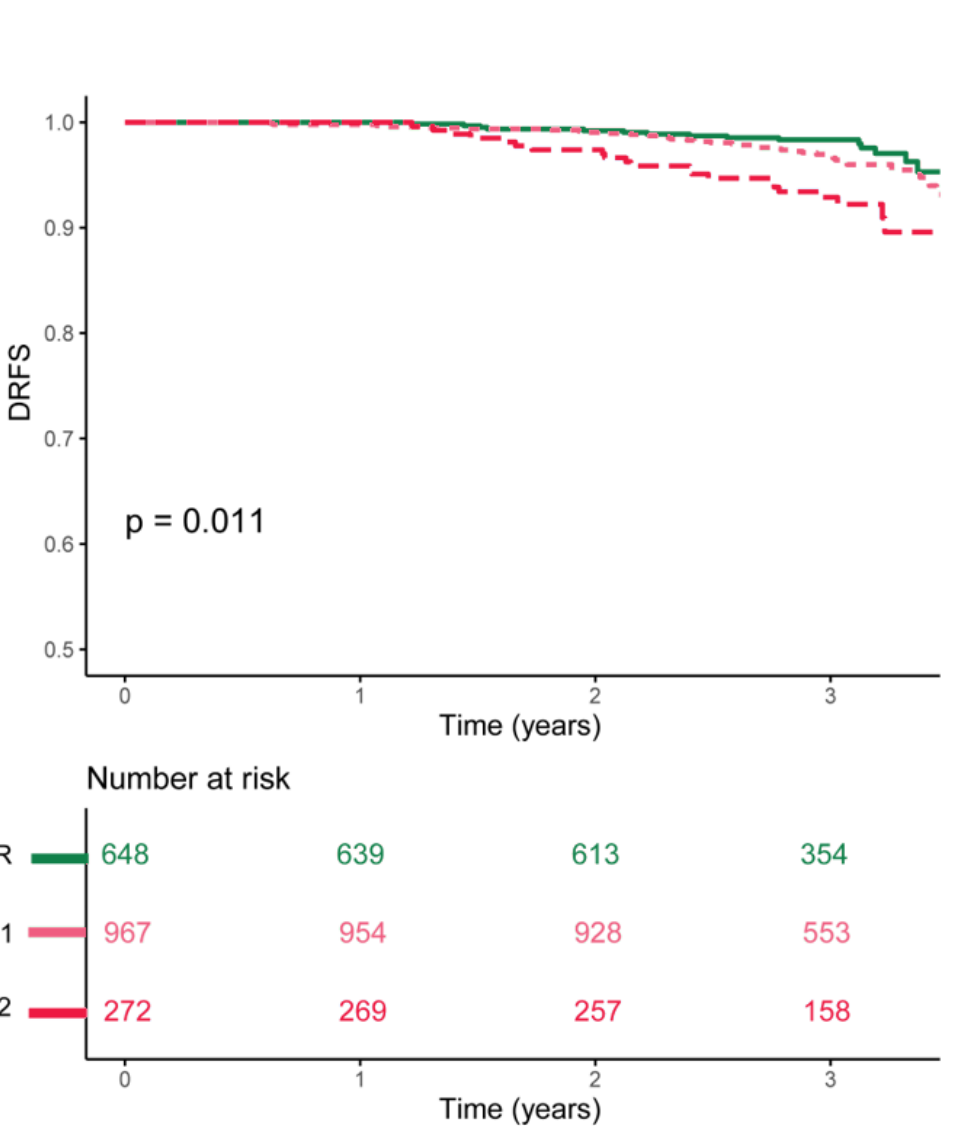


Figure 3. 3-year DRFS by MammaPrint within Ki67≥20% Patients (UL+L, H1 and H2)



Disclosure Statement: The presenting author has no conflicts of interest.

Results

- Among tumors with Ki67 ≥20% (n=1,887), 34% were classified as UltraLow (UL) or Low Risk (LR) by MammaPrint®.

- All MammaPrint risk groups were observed across the Ki67 spectrum, including High 1 and High 2 tumors at low Ki67 levels (Figure 1).

- In the Ki67 ≥20% cohort, 3-year distant recurrence-free survival (DRFS) was significantly higher for Low risk vs. High risk and UL+LR tumors vs. H2 tumors (98.3% vs 92.9%; absolute difference 5.4%, p=0.011), albeit short follow up time (Figure 2 and 3).

- In the overall study population, both MammaPrint High Risk and Ki67 ≥20% were prognostic in univariable analyses. (Table 2).

- In the multivariable analysis, MammaPrint remained independently prognostic, whereas Ki67 did not (H2 vs UL+LR: HR 2.46; p=0.005; Table 2).

- Within the Ki67 ≥20% subgroup, H2 tumors were associated with significantly worse DRFS compared with UL+LR tumors in univariable analysis (HR 2.31; p=0.003; Table 2).

- In the multivariable analysis of the Ki67 ≥20% subgroup, MammaPrint H2 remained independently prognostic, with a >2-fold increased risk of distant recurrence versus UL+LR (HR 2.33; p=0.026; Table 2).

Conclusions

- In HR+/HER2- early breast cancer with Ki67 ≥20%, MammaPrint identified a distinct low-risk subgroup predominantly treated without chemotherapy with favorable outcomes despite high proliferative activity.

- MammaPrint Low-Risk tumors were frequently observed across all Ki67 levels, including among tumors with high Ki67 expression

- Genomic risk stratification provided prognostic information beyond Ki67 and may help identify patients with favorable prognosis despite elevated Ki67, supporting more individualized chemotherapy decision-making.