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Impact of Germline *BRCA1* and *BRCA2* Mutations on 70-Gene Signature Risk for Patients Enrolled in the FLEX Study

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Poster 564P | Breast cancer, early stage
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Background

- Germline *BRCA1* and *BRCA2* pathogenic variants are associated with distinct clinicopathologic features: patients with *BRCA1* mutation have more often high grade and triple-negative tumors, and patients with *BRCA2* mutation more often have hormone receptor positive tumors (HR+).¹
- Since 2024, ASCO-SSO guidelines recommend offering *BRCA1/2* testing to all patients newly diagnosed with breast cancer at age ≤65, expanding the population with known germline status.²
- Data on 70-gene MammaPrint® (MP) risk and 80-gene Blueprint® (BP) molecular subtype in patients with germline *BRCA1/2* mutations are limited. These genomic classifications are distinct from clinical subtype defined by receptor status.
- We evaluated MP/BP classification by germline *BRCA1/2* status in FLEX, overall and within HR+HER2– disease.

Methods

Study Cohort

- Patients enrolled in the prospective, real-world, observational FLEX Study (NCT03053193) with MP/BP testing and reported germline *BRCA1/2* status were included.
- Patients with pathogenic *BRCA1* (n=85) or *BRCA2* (n=105) mutations were compared with a reference group with no known pathogenic germline mutation (n=3,148). Variants of uncertain significance (VUS; n=12) and patients with both *BRCA1* and *BRCA2* mutations (n=4) or discordant reports (n=6) were excluded.
- Analyses were performed across all clinical subtypes (N=3,338) and within HR+HER2– disease (N=2,484).

Statistics

Chi-square tests (categorical variables) and ANOVA (age) compared groups, excluding unknown values; p<0.05 was considered significant.

Table 1. Clinical characteristics by germline BRCA status in all clinical subtypes and in HR+HER2– disease

Characteristic	All clinical subtypes (N=3,338)				HR+HER2– (N=2,484)			
	<i>BRCA1</i> (N=85)	<i>BRCA2</i> (N=105)	No mutation (N=3,148)	p-value	<i>BRCA1</i> (N=58)	<i>BRCA2</i> (N=72)	No mutation (N=2,354)	p-value
Age, years				<0.001				<0.001
Mean (SD)	49.7 (13.9)	54.4 (11.6)	56.8 (12.5)		50.1 (13.7)	53.3 (12.0)	57.0 (12.3)	
<50	44 (51.8%)	40 (38.1%)	969 (30.8%)		30 (51.7%)	31 (43.1%)	712 (30.2%)	
50-64	26 (30.6%)	40 (38.1%)	1205 (38.3%)		19 (32.8%)	25 (34.7%)	904 (38.4%)	
≥65	14 (16.5%)	23 (21.9%)	946 (30.1%)		9 (15.5%)	15 (20.8%)	714 (30.3%)	
Male sex, n (%)	5 (5.9%)	5 (4.8%)	32 (1.0%)	<0.001	1 (1.7%)	3 (4.2%)	25 (1.1%)	0.050
Menopausal status				<0.001				<0.001
Pre-/Perimenopausal	43 (50.6%)	32 (30.5%)	965 (30.7%)		31 (53.4%)	24 (33.3%)	730 (31.0%)	
Postmenopausal	31 (36.5%)	63 (60.0%)	1991 (63.2%)		23 (39.7%)	42 (58.3%)	1488 (63.2%)	
Race/ethnicity				0.075				0.165
White	58 (68.2%)	61 (58.1%)	2324 (73.8%)		43 (74.1%)	43 (59.7%)	1766 (75.0%)	
Black	8 (9.4%)	11 (10.5%)	281 (8.9%)		3 (5.2%)	8 (11.1%)	205 (8.7%)	
Latin American	11 (12.9%)	18 (17.1%)	277 (8.8%)		6 (10.3%)	12 (16.7%)	194 (8.2%)	
AAPI	2 (2.4%)	3 (2.9%)	72 (2.3%)		2 (3.4%)	2 (2.8%)	46 (2.0%)	
Other	0 (0.0%)	1 (1.0%)	23 (0.7%)		0 (0.0%)	1 (1.4%)	14 (0.6%)	
Histology				0.271				0.495
IDC	71 (83.5%)	79 (75.2%)	2468 (78.4%)		50 (86.2%)	59 (81.9%)	1851 (78.6%)	
ILC	4 (4.7%)	12 (11.4%)	365 (11.6%)		4 (6.9%)	8 (11.1%)	313 (13.3%)	
Mixed IDC/ILC	5 (5.9%)	3 (2.9%)	142 (4.5%)		4 (6.9%)	2 (2.8%)	119 (5.1%)	
Other	0 (0.0%)	3 (2.9%)	104 (3.3%)		0 (0.0%)	1 (1.4%)	59 (2.5%)	
Tumor size				0.203				0.292
T1	24 (28.2%)	33 (31.4%)	1157 (36.8%)		19 (32.8%)	23 (31.9%)	945 (40.1%)	
T2	25 (29.4%)	20 (19.0%)	591 (18.8%)		18 (31.0%)	14 (19.4%)	411 (17.5%)	
T3	2 (2.4%)	3 (2.9%)	94 (3.0%)		2 (3.4%)	2 (2.8%)	66 (2.8%)	
T4	2 (2.4%)	0 (0.0%)	43 (1.4%)		1 (1.7%)	0 (0.0%)	27 (1.1%)	
Nodal status				0.003				<0.001
LN–	30 (35.3%)	38 (36.2%)	1420 (45.1%)		21 (36.2%)	28 (38.9%)	1104 (46.9%)	
LN+	21 (24.7%)	13 (12.4%)	383 (12.2%)		17 (29.3%)	9 (12.5%)	277 (11.8%)	
Grade				<0.001				<0.001
G1	7 (8.2%)	11 (10.5%)	768 (24.4%)		7 (12.1%)	7 (9.7%)	683 (29.0%)	
G2	24 (28.2%)	43 (41.0%)	1513 (48.1%)		21 (36.2%)	34 (47.2%)	1221 (51.9%)	
G3	48 (56.5%)	42 (40.0%)	629 (20.0%)		29 (50.0%)	29 (40.3%)	324 (13.8%)	
Ki-67				<0.001				<0.001
≤10%	4 (4.7%)	8 (7.6%)	669 (21.3%)		4 (6.9%)	6 (8.3%)	597 (25.4%)	
11-20%	8 (9.4%)	13 (12.4%)	537 (17.1%)		7 (12.1%)	8 (11.1%)	456 (19.4%)	
>20%	47 (55.3%)	45 (42.9%)	967 (30.7%)		33 (56.9%)	33 (45.8%)	618 (26.3%)	
ER staining				<0.001				<0.001
<10%	7 (8.2%)	2 (1.9%)	36 (1.1%)		7 (12.1%)	2 (2.8%)	28 (1.2%)	
10-29%	7 (8.2%)	3 (2.9%)	57 (1.8%)		6 (10.3%)	3 (4.2%)	41 (1.7%)	
≥30%	47 (55.3%)	81 (77.1%)	2601 (82.6%)		43 (74.1%)	63 (87.5%)	2234 (94.9%)	
PR status				<0.001				<0.001
Positive	42 (49.4%)	73 (69.5%)	2416 (76.7%)		40 (69.0%)	57 (79.2%)	2091 (88.8%)	
Negative	36 (42.4%)	24 (22.9%)	580 (18.4%)		17 (29.3%)	14 (19.4%)	255 (10.8%)	
Clinical subtype				0.001				-
HR+HER2–	58 (68.2%)	72 (68.6%)	2354 (74.8%)		58 (100%)	72 (100%)	2354 (100%)	
TNBC	14 (16.5%)	6 (5.7%)	199 (6.3%)		-	-	-	
HR+HER2+	1 (1.2%)	8 (7.6%)	195 (6.2%)		-	-	-	
HR–HER2+	2 (2.4%)	0 (0.0%)	58 (1.8%)		-	-	-	
Other	4 (4.7%)	10 (9.5%)	143 (4.5%)		-	-	-	

Data presented as n (%) unless otherwise indicated. Percentages use all patients in each group as the denominator; unknown values are not shown, so categories may not sum to 100%. p-values exclude unknowns; bold indicates p<0.05. BMI category did not differ (p=0.579, all; p=0.777, HR+HER2–). AAPI, Asian American and Pacific Islander; ER, estrogen receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LN, lymph node; PR, progesterone receptor; SD, standard deviation; TNBC, triple-negative breast cancer.

Figure 1. MammaPrint risk classification by germline BRCA status

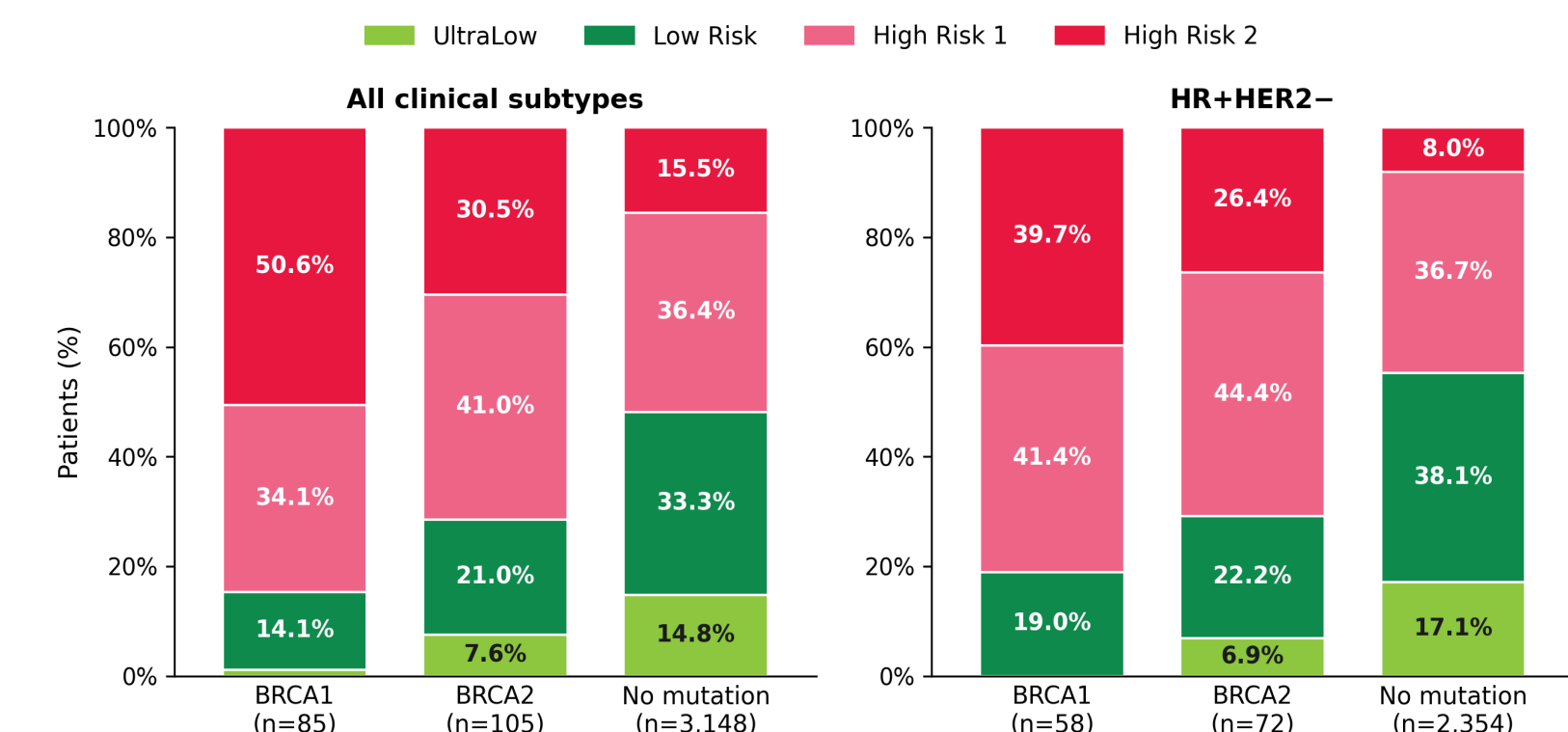


Figure 2. Blueprint molecular subtype by germline BRCA status

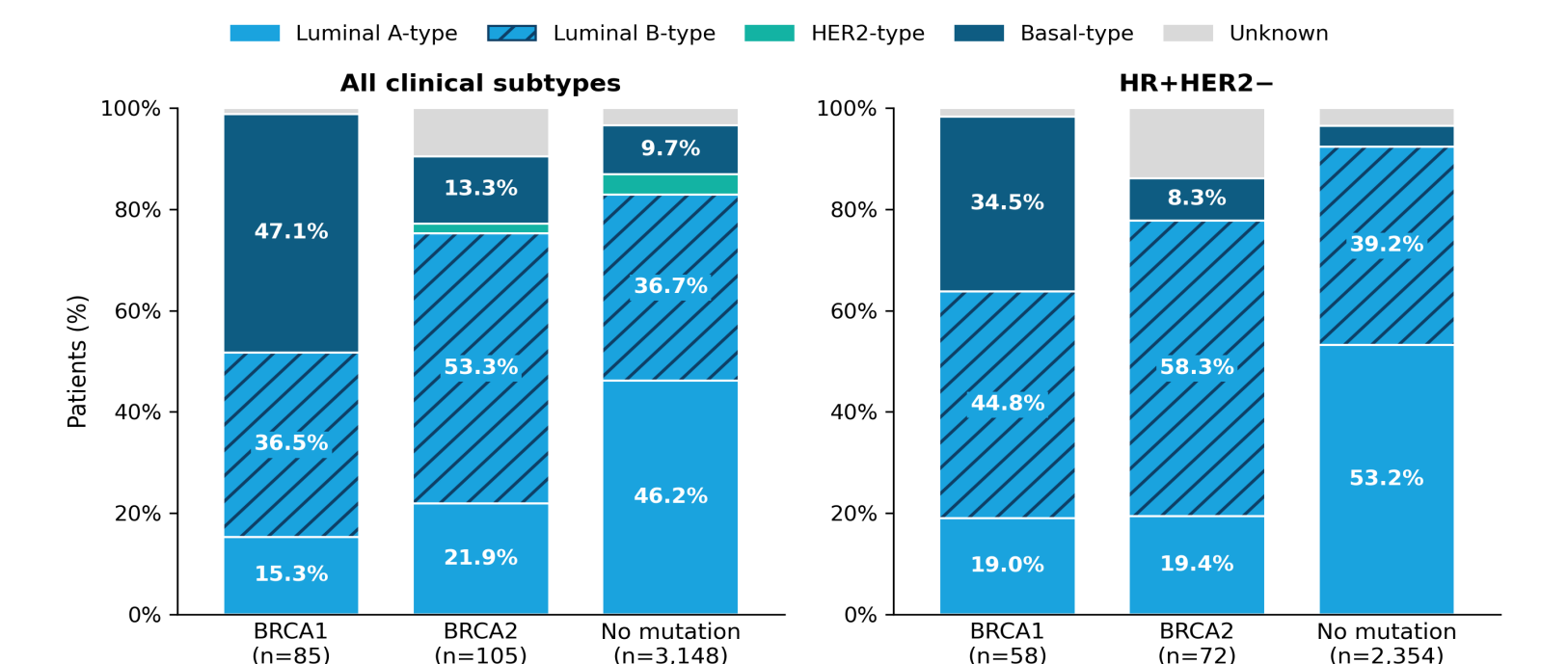
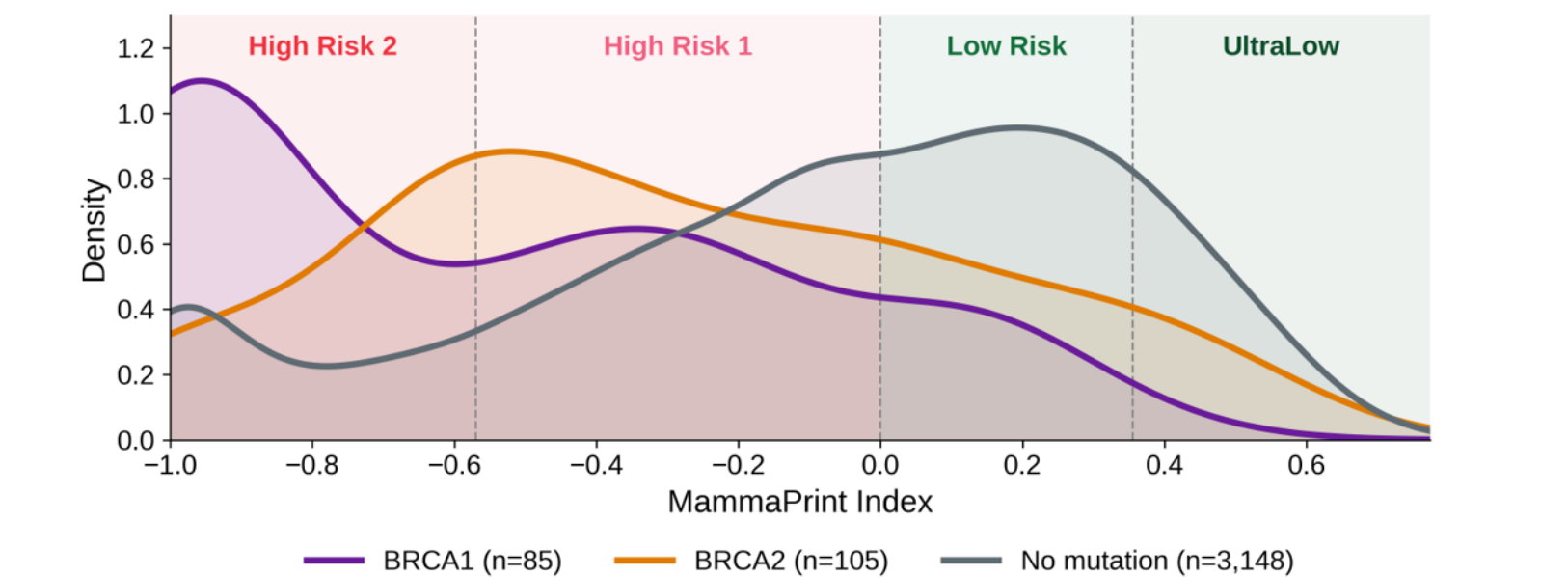
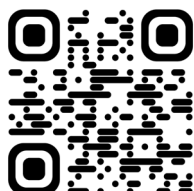


Figure 3. MammaPrint Index distribution (all clinical subtypes)



References: ¹Mavaddat N, et al. Cancer Epidemiol Biomarkers Prev. 2012;21:134-47. ²Bedrosian I, et al. J Clin Oncol. 2024;42:584-604.



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Results

- Of 3,338 patients, 85 (2.5%) had *BRCA1* and 105 (3.1%) had *BRCA2* mutations. HR+HER2– was the most common subtype in every group; TNBC was enriched with *BRCA1* (16.5%) compared with *BRCA2* (5.7%) and no mutation (6.3%; p=0.001) (Table 1).
- Patients with *BRCA1* mutations were younger (51.8%) and more often pre-/perimenopausal (50.6%), with more G3 (56.5%) and Ki-67 >20% (55.3%) tumors (all p<0.001).
- Patients with MP H2 tumors were more frequently seen in BRCA1 mutations (50.6%), followed by BRCA2 (30.5%), and no mutation (15.5%)(Figure 1).
- BP Basal was the most frequent subtype among patients with BRCA1 mutations (47.1%; p<0.001), whereas Luminal B was the most frequent subtype among patients with BRCA2 mutations (53.3%; p<0.001) (Figure 2).
- Within HR+/HER2– disease, MP H2 frequencies were 39.7% (BRCA1), 26.4% (BRCA2), and 8.0% (non-mutated); BP Basal-type frequencies were 34.5%, 8.3%, and 3.9% respectively (p<0.001).
- Within HR+/HER– disease, 34.5% of patients with *BRCA1* mutation had Basal-type tumors, whereas 58.3% of patients with *BRCA2* mutation had Luminal B-type tumors.
- Tumors from patients with BRCA1 mutation were enriched in the High Risk 2 region of the MP Index, whereas tumors from patients with BRCA2 mutation clustered predominantly within High Risk 1. In contrast, tumors from patients without BRCA mutations were most frequently observed in the Low-Risk region (Figure 3).

Conclusions

- Patients with BRCA1 mutation were enriched for MP High Risk 2 and BP Basal-type tumors, whereas BRCA2-mutated tumors more frequently exhibited MP High Risk 1 and BP Luminal B biology.
- Within HR+/HER2– disease, BP Basal-type tumors remained substantially more common among patients with BRCA1 mutation than among patients with BRCA2 mutation or no mutation, underscoring biologic heterogeneity beyond clinical subtype.
- Germline BRCA status was associated with distinct genomic risk patterns, supporting the value of integrating germline and tumor genomic profiling.
- Future FLEX analyses will evaluate how integration of germline BRCA status and genomic subtyping relates to treatment sensitivity and long-term clinical outcomes.