Independent Validation of a Pathology-Based Multimodal Artificial Intelligence Biomarker for Predicting Risk of Distant Metastasis in Postmenopausal, Estrogen Receptor-Positive, Early-Stage Breast Cancer Patients: Analysis of the ABCSG Trial 8

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Background

- Genomic assays are currently used to determine prognosis and predict treatment outcome in patients with estrogen receptor-positive (ER+), HER2-negative early breast cancer (EBC). However, their use is expensive, time-consuming and not available in many clinical facilities.
- We previously developed a multimodal artificial intelligence (MMAI) model (**Figure 1)** using clinical and histopathological data from more than 12,000 patients from six phase III trials, offering a faster, non-genomic alternative for personalized risk stratification.
- We present the first external independent validation of this MMAI model using the ABCSG trial 8 - a large, prospective phase III trial of a low- to moderate-risk cohort of ER+ postmenopausal breast cancer patients receiving endocrine therapy (ET) only - to assess its prognostic performance for distant metastasis (DM).

Objective

Externally validate locked MMAI model (Presentation PD11-01) in ABCSG-8 for prognostic risk of DM

Methods and Materials

ER+ HER2- patients from the prospective-randomized trial ABCSG-8 with digitized baseline H&E-stained sections, complete clinical data (age, tumor size and nodal status), and long-term follow up were included in this pivotal validation study (**Figure 2)**. The locked MMAI model includes a continuous score and predefined risk groups. Prognostic performance was assessed using univariable and multivariable Cox proportional hazard models, with hazard ratios (HR) and corresponding 95% confidence intervals (CI).

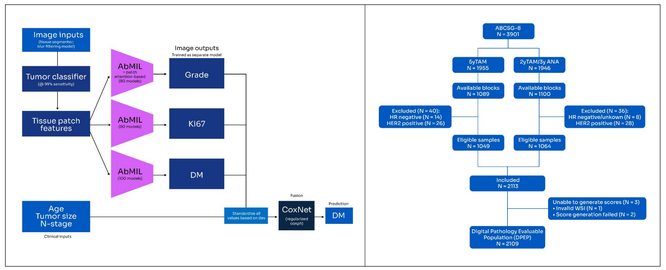


Figure 1. MMAI architecture of the breast model.

Figure 2 Flowchart showing patient selection and sample collection is shown in ABCSG-8

Characteristic	Low Risk N = 1,629[1]	Intermediate Risk N = 181[1]	High Risk N = 299[1]	Total N = 2109[1]
Age (years)				
Mean (SD)	64 (8)	65 (9)	64 (8)	64 (8)
T-Stage, n (%)				
pT1	1,316.0 (80.8%)	104.0 (57.5%)	124.0 (41.5%)	1,544.0 (73.2%)
pT2	311.0 (19.1%)	74.0 (40.9%)	161.0 (53.8%)	546.0 (25.9%)
pT3	2.0 (0.1%)	3.0 (1.7%)	14.0 (4.7%)	19.0 (0.9%)
Tumor Size (cm)				
Mean (SD)	1.5 (0.7)	2.0 (1.1)	2.4 (1.3)	1.7 (0.9)
Nodal Status, n (%)				
pN0	1,349.0 (82.8%)	104.0 (57.5%)	92.0 (30.8%)	1,545.0 (73.3%)
pN1	270.0 (16.6%)	72.0 (39.8%)	157.0 (52.5%)	499.0 (23.7%)
pN2-3	10.0 (0.6%)	5.0 (2.8%)	50.0 (16.7%)	65.0 (3.1%)
Grading, n (%)				
G1	400.0 (24.6%)	17.0 (9.4%)	22.0 (7.4%)	439.0 (20.8%)
G2	1,136.0 (69.7%)	151.0 (83.4%)	249.0 (83.3%)	1,536.0 (72.8%)
GX	93.0 (5.7%)	13.0 (7.2%)	28.0 (9.4%)	134.0 (6.4%)
Histology, n (%)				
Ductal	1,205.0 (74.0%)	125.0 (69.1%)	209.0 (69.9%)	1,539.0 (73.0%)
Lobular	289.0 (17.7%)	44.0 (24.3%)	70.0 (23.4%)	403.0 (19.1%)
Other	135.0 (8.3%)	12.0 (6.6%)	20.0 (6.7%)	167.0 (7.9%)
Estrogen Receptor, n (%)				
Positive	1,628.0 (99.9%)	180.0 (99.4%)	298.0 (99.7%)	2,106.0 (99.9%)
Negative	1.0 (0.1%)	1.0 (0.6%)	1.0 (0.3%)	3.0 (0.1%)
Progesterone Receptor, n (%)				
Positive	1,475.0 (90.5%)	160.0 (88.4%)	268.0 (89.6%)	1,903.0 (90.2%)
Negative	154.0 (9.5%)	21.0 (11.6%)	31.0 (10.4%)	206.0 (9.8%)
HER2, n (%)				
Negative	1,557.0 (100.0%)	181.0 (100.0%)	295.0 (100.0%)	2,033.0 (100.0%)
Missing	72 (4.4%)	0 (0%)	4 (1.3%)	76 (3.6%)
Ki67				
Median (Q1, Q3)	5.0 (1.0, 10.0)	10.0 (5.0, 10.0)	10.0 (5.0, 20.0)	5.0 (5.0, 10.0)
Low (≤5%)	878.0 (56.4%)	76.0 (42.0%)	87.0 (29.5%)	1,041.0 (51.2%)
Intermediate (6-29%)	642.0 (41.2%)	84.0 (46.4%)	178.0 (60.3%)	904.0 (44.5%)
High (≥30%)	37.0 (2.4%)	21.0 (11.6%)	30.0 (10.2%)	88.0 (4.3%)
Missing	72 (4.4%)	0 (0%)	4 (1.3%)	76 (3.6%)
Treatment Arm, n (%)				
2y TAM + 3y ANA	827.0 (50.8%)	86.0 (47.5%)	149.0 (49.8%)	1,062.0 (50.4%)
5y TAM	802.0 (49.2%)	95.0 (52.5%)	150.0 (50.2%)	1,047.0 (49.6%)

Table 1. Baseline characteristics.

Results

MMAI raw scores were generated for 2,109 patients. The median follow-up time was 9.5 years. Despite the overall lower risk profile (G1 and G2 only) of the ET-only population **(Table 1),** the MMAI classified 77% patients as low risk, 9% as intermediate risk, and 14% as high risk**.** The estimated 10-year DM-free rates were 94.7% (93.3% - 95.8%) for low-risk patients, 89.1% (82.5% - 93.3%) for intermediate-risk patients, and 77.3% (71.3% - 82.2%) for high-risk patients **(Figure 3).** In univariable analysis (UVA), both the continuous MMAI raw score and MMAI risk groups were significantly associated with risk of DM: MMAI raw score (HR [95% CI] = 2.22 [1.91 - 2.58], p<0.001) and MMAI risk group (intermediate vs. low risk HR [95% CI] = 2.19 [1.34 - 3.57], p=0.002; high vs. low risk HR [95% CI] = 4.45 [3.19 - 6.19], p<0.001) **(Table 2).** In multivariable analysis (MVA) adjusting for age, tumor size, nodal status, both continuous MMAI raw score (p<0.001) and MMAI risk group (p<0.001) remained independently associated with DM **(Table 3).** The MMAI raw score remained significantly associated with the risk of DM across clinically meaningful subgroups, including lymph node status (N0 and N1), tumor grade (Grade 1 and 2), histology (invasive ductal carcinoma and invasive lobular carcinoma), and trial-defined Ki67 levels (≤5%, 6-29%, ≥30%) **(Table 4).** Additionally, the image-only component of the MMAI was independently associated with risk of DM (p<0.001 in both UVA and MVA). The MMAI score showed a 10-year tdAUC of 0.73 (95% CI: 0.68–0.77) compared to 0.70 (95% CI: 0.66–0.75) for the clinical comparator model. MMAI model shows performance comparable to established multigene tests in an indirect comparison between MMAI and established multigene tests that were also validated in ABCSG 8 (**Table 5**).

Variable	Levels	HR (95% CI)	P-value
Age (years)		1.02 (1.00-1.04)	0.1
Tumor size		1.42 (1.30-1.54)	<0.001
T-Stage	T2 versus T1	3.10 (2.28-4.23)	<0.001
	T3 versus T1	4.57 (1.44-14.47)	0.01
Nodal status	N1 versus N0	2.54 (1.84-3.51)	<0.001
	N2-3 versus N0	4.55 (2.58-8.01)	<0.001
Grading		2.21 (1.35-3.61)	0.002
MMAI image-only score[1]		1.84 (1.56-2.16)	<0.001
MMAI risk score[2]		2.22 (1.91-2.58)	<0.001
MMAI risk group	Intermediate risk versus low risk	2.19 (1.34-3.57)	0.002
	High risk versus low risk	4.45 (3.19-6.19)	<0.001
	High risk versus low/intermediate risk	3.98 (2.90-5.47)	<.001
	Intermediate/high risk versus low risk	3.53 (2.60-4.80)	<0.001

[1]MMAI image-only score is per 1 SD increase, [2]MMAI risk score is per 1 SD increase

Table 2. Univariable Cox regression models for DM

Variable[1]	Levels	HR (95% CI)	LRT P-value
MMAI image-only score[2]		1.68 (1.42-1.98)	<0.001
MMAI raw risk score[3]		1.92 (1.57-2.34)	<0.001
MMAI risk group	Intermediate risk versus low risk	1.63 (0.98-2.71)	<0.001
	High risk versus low risk	2.72 (1.81-4.07)	<0.001
	High risk versus low/intermediate risk	2.41 (1.64-3.53)	<0.001
	Intermediate/high risk versus low risk	2.23 (1.56-3.21)	<0.001

[1]Age, tumor size, and N status were adjusted in the regression, [2]MMAI image-only score is per 1 SD increase, [3]MMAI raw risk score is per 1 SD increase

Table 3. Multivariable Cox regression models for DM

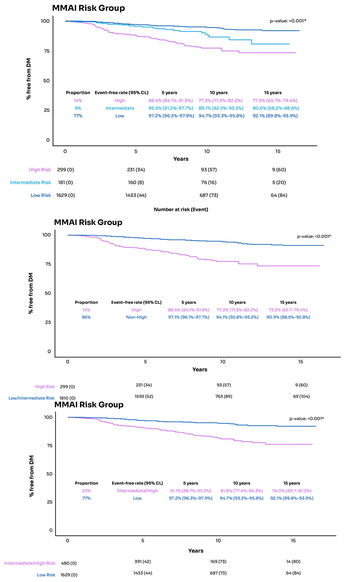


Figure 3. Kaplan-Meier curves of MMAI risk groups

Subgroup	Sublevels	N (# of event)	HR (95% CI)
Age	<60	713 (51)	2.22 (1.68-2.92)
	≥60	1396 (113)	2.21 (1.84-2.65)
T-Stage	pT1	1544 (80)	2.04 (1.60-2.61)
	pT2	546 (81)	1.94 (1.52-2.47)
	pT3	19 (3)	4.03 (0.70-23.21)
Nodal Status	pN0	1545 (84)	2.04 (1.58-2.65)
	pN1	499 (66)	2.29 (1.70-3.08)
	pN2-3	65 (14)	1.59 (0.87-2.91)
Grading	G1	439 (18)	2.56 (1.62-4.07)
	G2	1536 (137)	2.14 (1.80-2.55)
	GX	134 (9)	2.27 (1.32-3.89)
Histology	Ductal	1539 (118)	2.17 (1.81-2.60)
	Lobular	403 (36)	2.22 (1.62-3.04)
	Other	167 (10)	2.98 (1.53-5.82)
Ki67	Low (≤5%)	1041 (52)	2.26 (1.77-2.88)
	Intermediate (6-29%)	904 (92)	1.84 (1.47-2.30)
	High (≥30%)	88 (16)	4.04 (1.99-8.22)
Type of Surgery	Breast conserving	1742 (119)	2.30 (1.89-2.80)
	Mastectomy	367 (45)	1.96 (1.50-2.56)
Treatment Arm	5y TAM	1047 (85)	1.97 (1.60-2.42)
	2y TAM + 3y ANA	1062 (79)	2.58 (2.06-3.25)

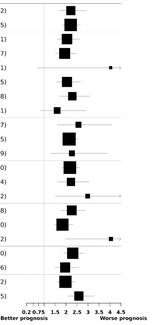


Table 4. Subgroups analyses

Test	No. of ER+HER2- ABCSG-8 patients	10-year DM risk Low risk / High risk	% classified as low risk	HR (95%CI)	P-value
EndoPredict[8]	1324	4.0% / 22.0%	65%	4.3 (2.7-6.7)	<0.001
Prosigna[6]	1397	3.4% / 20.1%	35%	4.3 (2.4-7.4)	<0.001
MammaPrint[5]	658	8.7% / 15.2%	78%	1.9 (1.1-3.3)	0.019
OncoMaSTR[11]	1056	5.8% / 21.5%	78%	4.4 (2.9-6.7)	<0.001
MMAI model	2109	5.3% / 22.6%	77%	4.5 (3.2-6.2)	<0.001

Table 5. Comparison of the MMAI model with multigene tests validated in ABCSG-8

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Conclusions

This study validates the MMAI model, originally developed for HR+ HER2- EBC, as a strong prognostic tool for DM in lower-risk postmenopausal women with ER+ HER2- EBC. This MMAI technology promises to improve personalized risk stratification and adjuvant treatment decisions in ER+ HER2- EBC as a cost-effective, non-tissue consuming, and faster alternative to genomic assays.

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