Comparative performance of an AI-based digital pathology tool and genomic signatures in early ER+/HER2- breast cancer

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Background

→ Prognostic tools, such as genomic signatures, are important for **guiding adjuvant therapy in early breast cancer** (EBC), particularly for patients with estrogen receptor-positive, HER2-negative (**ER+/HER2-**) tumors, where optimizing the treatment strategy, like making a de-escalation decision, remains a clinical challenge [1]).

→ Recent advances in artificial intelligence (AI) applied to whole-slide images (WSI) have opened new possibilities for capturing prognostic information directly from **routinely available H&E slides** of invasive breast tumors.

→ This may offer a scalable, cost-effective, and accessible approach to **personalized risk assessment**.

Objective

→ Evaluate the prognostic performance of **RlapsRisk BC**, an AI digital pathology-based tool developed to estimate the risk of distant recurrence, in comparison with **EndoPredict** (EP) [3] and **Oncotype DX** (ODX) [4], using five-years distant recurrence-free survival (dRFS) as the primary endpoint.

Data

Cohort		MDA (MD Anderson, USA)		GR (Gustave Roussy, FR)	
n_{TOTAL} (n_{events})		154 (42)		381 (7)	
Age	<50 y.o	61	39.6%	108	28.35%
	>50 y.o	93	60.4%	273	71.65%
Histological grade	Grade 1	35	22.7%	23	6.04%
	Grade 2	89	57.8%	277	72.7%
	Grade 3	30	19.5%	81	21.3%
Nodal status	N-	154	100%	283	74.3%
	N+	0	0%	98	25.7%
Tumor size	pT1	99	64.3%	248	65.1%
	pT2/3/4	55	35.7%	133	34.9%
	mean SD(mm)	19.59 ± 12.29		19.83 ± 9.41	
Adjuvant treatment	ET** only	154	100%	180	47.2%
	ET + chemo	0	N/A	201	52.8%
Routine test result*	Low Risk	96	62.3%	128	32.6%
	High Risk	58	37.7%	257	67.4%

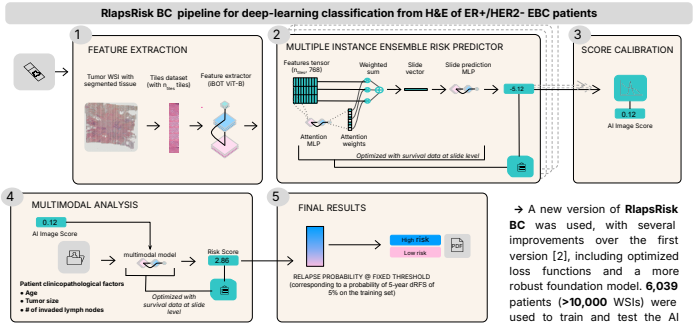
→ Two independent retrospective cohorts of ER+/HER2- EBC patients who underwent genomic testing as part of their **routine clinical care**.

→ For both cohorts, the median clinical follow-up is **more than 5 years** (MDA: 67.81 months; GR: 61.51 months).

→ Diagnostic H&E-stained slides from **surgical resection specimens** were digitized at x20.

**ODX on MDA, EP on GR*
*** Endocrine Therapy*

Method



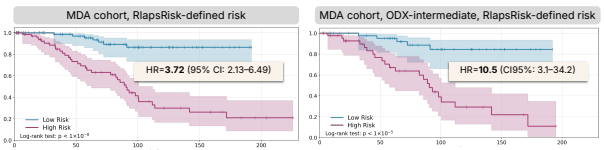
→ For **ODX**, patients were considered high risk based on standard thresholds: a recurrence score (RS) ≥25 for postmenopausal patients and ≥16 for premenopausal patients [5]; for the intermediate category: a RS from 11 to 25 [6].

→ For **EP**, we used the validated EPclin cutoff of 3.3 to define the high risk subgroup [7].

→ A new version of **RlapsRisk BC** was used, with several improvements over the first version [2], including optimized loss functions and a more robust foundation model. **6,039** patients (**>10,000** WSIs) were used to train and test the AI model, which was **locked and integrated into a product before results generation** on the study cohorts.

Results

Kaplan Meier Analyses

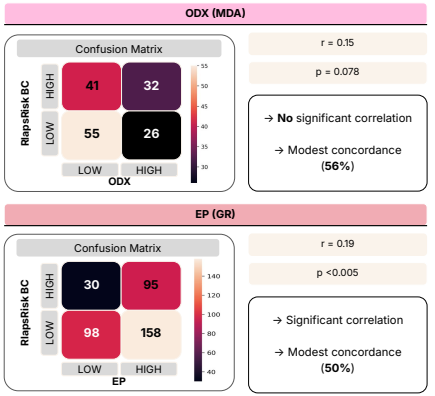


→ 50% of ODX-intermediate classified low risk by RlapsRisk BC

→ Potential for enhanced decision support

Results

Comparison metrics



Prognostic performances metrics

Metric	RlapsRisk BC (MDA)	ODX (MDA)	RlapsRisk BC (GR)	EP (GR)
AUC	0.78	0.53	0.73	0.57
% classified as low-risk	52.6%	62.3%	67%	34%
% distant recurrence events in low-risk group at 5y	4.7%	19.8%	0.4%	1.7%
% distant recurrence events in high-risk group at 5y	34.7%	16%	3.7%	1.4%

In both settings:

→ Stronger discriminative power

→ Better alignment with observed risk

RlapsRisk BC high-risk classification captured the majority of observed events in both cohorts: 6 of 7 in GR and 35 of 42 in MDA.

Conclusion

These findings suggest that RlasRisk BC may support treatment de-escalation by safely expanding the proportion of patients classified as low risk who experience excellent outcomes within their risk group, while also improving identification of patients with a genuinely higher likelihood of recurrence.

This ability to **improve risk stratification** makes it a promising tissue-efficient alternative or complementary option to current genomic assays such as ODX and EP in ER+/HER2– early breast cancer.

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