Clinical validation of an AI-digital pathology-based prognostic test to predict risk of recurrence using biopsy specimens from patients with invasive breast cancer (IBC)

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INTRODUCTION

- Standard of care genomic testing guides adjuvant treatment decisions for early-stage HR+/HER2- IBC.
- Reliable prognostic testing with biopsy specimens is needed to personalize management in the neoadjuvant setting and potentially enable earlier adjuvant decisions.
- This study clinically validated the PreciseBreast Biopsy test (PDxBRBx), incorporating age and morphologic features, to predict recurrence risk.

METHODS

Patients:

- 1788 patients (pts) with IBC from the Mount Sinai Health System (2004-2016) with median follow-up of 6 years.

PDxBRBx Test & Performance Analysis:

- 60%-40% balanced training (surgical) and validation (biopsy) cohorts
- PDxBRBx was performed using H&E stained slides imaged (40X) with a Philips Ultra-Fast scanner. An AI-enabled platform deconstructed images to quantify tumor cell & tissue architectural features.
- Age is algorithmically combined with 8 morphologic features (AI-grade model) generating PDxBRBx risk scores (0-100) to stratify pts into low (<73) or high (≥73) risk of recurrence.
- Risk stratification for invasive breast cancer free survival (IBCFS) was assessed by concordance index (C-index), area under the curve (AUC), Kaplan-Meier analysis, hazards ratios (HR), sensitivity (Se), specificity (Sp), negative predictive value (NPV), & positive predictive value (PPV).
- Matched excisional specimens from PreciseBreast (PDxBR) cohort were evaluated for risk score correlation using Cohen's Kappa and Odds Ratio.

Table 1. Patient Characteristics

Total Cohort	Training (n=1012)	Validation (n=776)
Age at Diagnosis, years, median (SD)	59 (25-90)	60 (24-90)
≤50, n (%)	292 (28.9)	197 (25.4)
>50, n (%)	720 (71.1)	579 (74.6)
Race		
White	561 (55.4)	445 (57.4)
Black	54 (5.3)	37 (4.8)
Asian	5 (0.5)	8 (1)
Other	103 (10.2)	119 (15.3)
Unknown	289 (28.6)	167 (21.5)
Tumor Size, cm		
≤2.5 cm	897 (88.6)	693 (89.3)
>2.5 to ≤5	105 (10.4)	72 (9.3)
>5	10 (1)	11 (1.4)
Anatomic Stage, n (%)		
I	694 (68.6)	523 (67.5)
II	245 (24.2)	193 (24.9)
III	73 (7.2)	59 (7.6)
Lymph Node, n (%)		
Negative	783 (77.4)	662 (85.3)
Positive 1-3	229 (22.6)	114 (14.7)
Tumor Grade, n (%)		
1	206 (20.4)	111 (14.3)
2	411 (40.6)	337 (43.4)
3	395 (39)	328 (42.3)
ER Status		
Positive	881 (87.1)	672 (86.6)
Negative	131 (12.9)	104 (13.4)
PR Status		
Positive	819 (80.9)	632 (81.4)
Negative	193 (19.1)	144 (18.6)
HER2 Status		
IHC 3+	125 (12.3)	97 (12.5)
IHC 0, 1+, or 2+ (FISH neg)	887 (87.7)	679 (87.5)
Treatments Received, n (%)		
Chemotherapy	372 (36.8)	317 (40.9)
Endocrine Therapy	607 (60)	532 (68.6)
Radiation Therapy	450 (44.5)	400 (51.6)
Total Events	145 (14.3)	106 (13.)

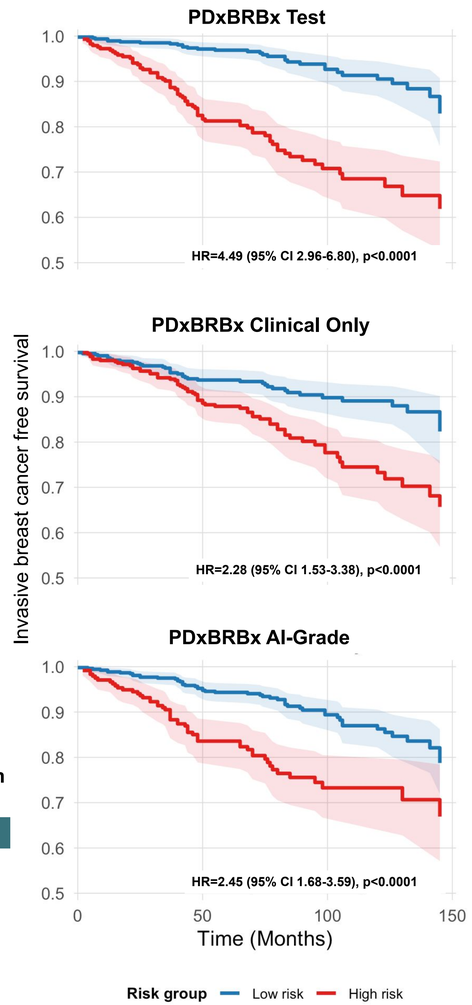
Table 2. PDxBRBx & PDxBR Scores Comparison from Matched Biopsy & Excisional Specimens

PDxBRBx and PDxBR Scores Agreement

	PDxBR Low-Risk	PDxBR High-Risk
PDxBRBx Low-Risk	382	19
PDxBRBx High-Risk	146	229

78.7% Concordance
Cohen's κ: 0.57 (0.51 - 0.62, p< 0.0001)
OR: 31.4 (18.77 - 55.08, p < 0.0001)

Figure 1. KM Survival Curves for PDxBRBx test, Clinical Only Model, & AI-Grade Model



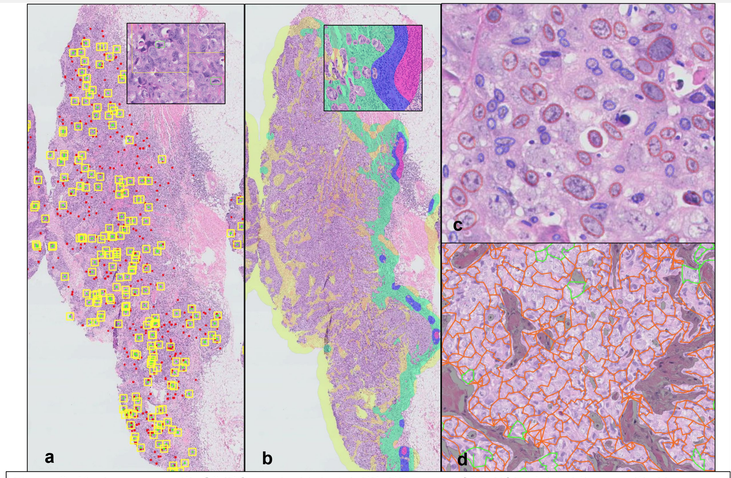


Figure 2. 41 y/o woman with G3 IDC, and a high risk PDxBR score of 90. H&E stained tissue with AI overlays: a) shows a low power view with yellow/green/red boxes identifying mitotic figures; insert shows high power. b) is a lymphocyte map, high density to low density (red>purple>green>yellow); insert high power. c) largest nuclei outlined in red, smaller in blue. d) orange overlay is high grade architecture, green low-grade architecture.

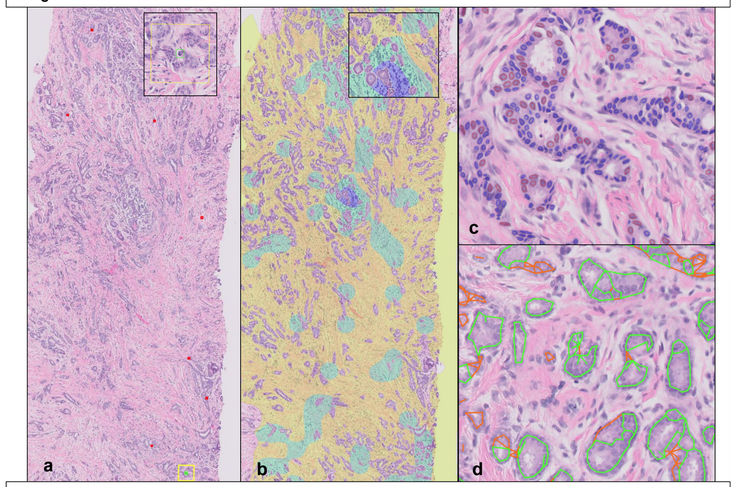


Figure 3. 46 y/o woman with G1 IDC, and a low risk PDxBR score of 30. H&E stained tissue with AI overlays: a) shows a low power view with yellow/green/red boxes identifying mitotic figures; insert shows high power. b) is a lymphocyte map, high density to low density (red>purple>green>yellow); insert high power. c) largest nuclei outlined in red, smaller in blue. d) orange overlay is high grade architecture, green low-grade architecture.

RESULTS

Training Cohort (n=1012):

- PDxBRBx (Age + AI-grade) yielded a C-index of 0.72 (95% CI, 0.69-0.78) vs age C-index 0.61 (95% CI, 0.55 - 0.66) vs AI-grade 0.69 (95% CI, 0.64 - 0.73), with Se 0.70, Sp 0.67, NPV 0.93, & PPV 0.25.
- PDxBRBx HR was 4.49 (95% CI 2.96 - 6.8, p<0.001) for predicting IBCFS

Validation Cohort (n=776)

- PDxBRBx yielded a C-index of 0.73 (95% CI, 0.69-0.78) vs age 0.64 (95% CI, 0.57-0.70) vs AI-grade 0.69 (95% CI, 0.64-0.74), with Se 0.70, Sp 0.67, NPV 0.93, and PPV 0.25.
- HRs for both PDxBRBx and AI-Grade were highly statistically significant.
- All individual morphologic biopsy features including mitotic figure quantitation, nuclear pleomorphism, tumor–stromal ratio, lymphocytic content, & tumor architecture were statistically significant predictors of event risk (all p<0.05, most p<0.001).

Substantial agreement was observed between PDxBRBx and matched excisional PDxBR risk scores.

CONCLUSIONS

- We clinically validated PreciseBreast Biopsy, an AI-based digital pathology test, which predicted IBCFS within 6 years.
- The test supports accurate clinical-pathologic risk assessment & patient management at diagnosis.
- Further studies in neoadjuvant and adjuvant settings will clarify the impact of these results on treatment selection.