# Biologic and Pathologic Correlations of the HER2DX Genomic Test in HER2+ Disease

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Abstract #PS3-10-24

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## Background

HER2DX is a validated genomic test used to optimize treatment decisions in early-stage HER2-positive (HER2+) breast cancer. It provides three scores: relapse risk, pathologic complete response (pCR), and *ERBB2* mRNA expression.

This study aimed to evaluate the association between HER2DX and histopathologic features and to assess its relationship with pCR after neoadjuvant therapy.

## Methods

The HER2DX genomic[1] test was evaluated on 410 formalin-fixed paraffin-embedded stage I-III HER2+ BC samples. Central assessment of hematoxylin and eosin (H&E)-stained slides included evaluation of tumor grade, histological subtype, stromal tumor-infiltrating lymphocytes (TILs), tertiary lymphoid structures (TLS), and spatial patterns of the tumor immune microenvironment (TIME). Local assessment included evaluation of hormone receptor (HR) status, Ki67 index, and HER2 immunohistochemistry (IHC) with or without in situ hybridization (ISH) testing. Clinical data were available for 250 patients who received neoadjuvant trastuzumab-based therapy.

Descriptive statistics were applied, and univariate and multivariable logistic regression analyses were conducted to identify factors associated with pCR after neoadjuvant trastuzumab-based therapy.

## Results

- The distribution of clinicopathological features is shown in **Table 1**.
- HER2DX scores distribution is presented in **Figure 1**.
- The HER2DX pCR score was significantly associated with all histopathological features evaluated. Previous studies have reported correlations between a high pCR score and grade 3 tumors, HER2 3+ status, HR-negative status, increased proliferation (Ki67%), and elevated TILs levels. In the present analysis, in addition to confirming these previously described associations, we also observed correlations between a high pCR score and both the presence of TLS and an inflamed-excluded pattern, representing interesting novel findings (**Figure 2**).
- The HER2DX risk score was significantly associated with several histopathological features. As previously reported, a high risk score correlated with HER2 3+, increased proliferation (Ki67%), and reduced TILs levels. In this study, we additionally identified novel associations between a high risk score, TLS absence, and a desert-excluded pattern (**Figure 3**).
- The HER2DX ERBB2 score was significantly associated with HR-negative and HER2 3+ status. The correlation between HER2 3+ IHC results and the ERBB2 score demonstrated substantial concordance (~81%; Cohen's kappa coefficient = 0.56) (**Figure 4**).
- Correlation analyses between HER2DX scores, HER2DX molecular signatures, and continuous pathological features (TILs and Ki67%) were performed (**Figure 5A**). Specifically, the HER2DX IgG signature showed a positive correlation with TIL levels, while the HER2DX proliferation signature correlated positively with Ki67 (**Figure 5B, C**).
- Overall, 36% achieved pCR. Univariate and multivariate analyses confirmed that the HER2DX pCR score is an independent predictor of pCR (**Table 2**).

References: (1) Prat A et al. Ebiomedicine, 2002

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## Results

**Table 1.** Clinicopathological cohort features

| | HER2DX samples (N = 410) |
|---|---|
| **Hospital participation, n (%)** | |
| Site 1 | 150 (36.6%) |
| Site 2 | 127 (31.0%) |
| Others | 133 (32.4%) |
| **Grade, n (%)** | |
| Grade 1 | 28 (6.8%) |
| Grade 2 | 208 (50.7%) |
| Grade 3 | 143 (34.9%) |
| NA | 31 (7.6%) |
| **HER2 IHC status, n (%)** | |
| HER2 2+/ISH+ | 109 (26.6%) |
| HER2 3+ | 298 (72.7%) |
| NA | 3 (0.7%) |
| **Hormone receptors, n (%)** | |
| HR- | 86 (21.0%) |
| HR+ | 268 (65.4%) |
| NA | 56 (13.6%) |
| **ki67 (%), median (range)** | 30 (<1-95) |
| **TILs (%), median (range)** | 6 (<1-90) |
| **TLS, n (%)** | |
| TLS absense | 238 (58.0%) |
| TLS presence | 166 (40.5%) |
| NA | 6 (1.5%) |
| **Spatial TIME Pattern, n (%)** | |
| Immune-desert | 221 (53.9%) |
| Immune-excluded | 40 (9.7%) |
| Immune-inflamed | 143 (34.9%) |
| NA | 6 (1.5%) |

* *NA = Not available*

**Figure 1.** Distribution of HER2DX (A) pCR score, (B) risk score and (C) ERBB2 score

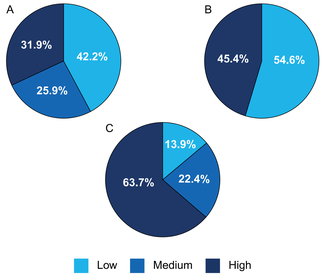



**Figure 2.** HER2DX pCR score association with (A) TLS status and (B) Spatial TIME pattern

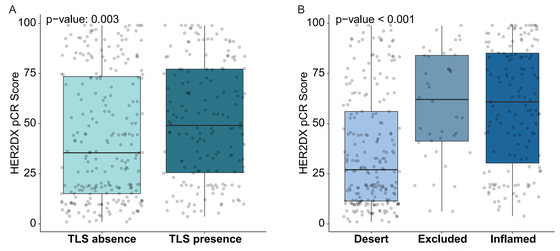



**Figure 3.** HER2DX risk score association with (A) TLS status and (B) Spatial TIME pattern

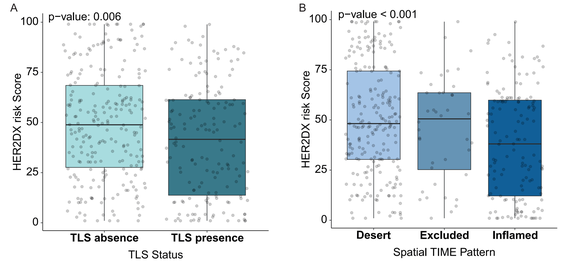



**Figure 4.** HER2DX ERBB2 score was associated with HR- negative and HER2 3+ status

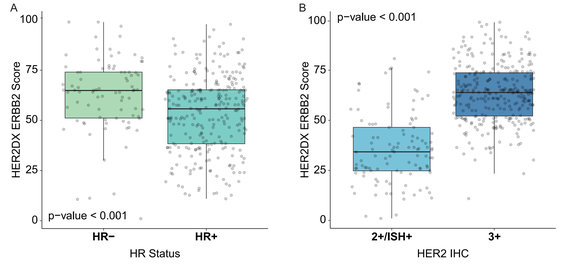



**Figure 5.** Correlations of HER2DX scores, HER2DX signatures and continous pathological features (TILs and Ki67 %)

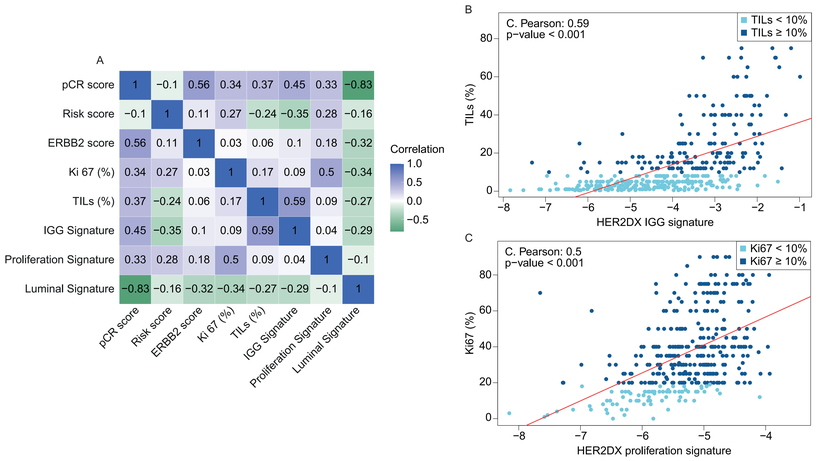



**Table 2.** Univariate and multivariable logistic regression models of factors associated with pCR

| | | | | Univariate | | Multivariate | |
|---|---|---|---|---|---|---|---|
| **Variable** | | **N** | **Odds ratio** | | **p** | | **p** |
| **Grade** | 1−2 | 154 | | Reference | | Reference | |
| | 3 | 82 | | 1.85 (1.07, 3.22) | 0.029 | 1.23 (0.59, 2.56) | 0.580 |
| **HER2 IHC status** | 2+/ISH+ | 57 | | Reference | | Reference | |
| | 3+ | 191 | | 3.39 (1.67, 7.47) | 0.001 | 2.77 (1.12, 7.50) | 0.030 |
| **HR status** | negative | 45 | | Reference | | Reference | |
| | positive | 164 | | 0.26 (0.13, 0.51) | <0.001 | 0.68 (0.28, 1.63) | 0.380 |
| **Ki67 % (cont.)** | | 240 | | 1.02 (1.00, 1.03) | 0.006 | 1.02 (1.00, 1.03) | 0.050 |
| **TILs % (cont.)** | | 248 | | 1.02 (1.00, 1.03) | 0.031 | 1.00 (0.97, 1.02) | 0.640 |
| **TLS status** | absence | 146 | | Reference | | | |
| | presence | 102 | | 1.03 (0.61, 1.74) | 0.915 | | |
| **Spatial TIME pattern** | others | 154 | | Reference | | | |
| | inflamed | 94 | | 1.18 (0.69, 2.01) | 0.536 | | |
| **Histology** | others | 24 | | Reference | | | |
| | ductal/NST | 226 | | 1.41 (0.58, 3.77) | 0.465 | | |
| **HER2DX pCR score (cont.)** | | 250 | | 2.25 (1.65, 3.14) | <0.001 | 1.77 (1.08, 2.97) | 0.030 |

0.2 0.5 1 2 5

## Conclusion

HER2DX reflects key biological and pathological features of HER2+ breast cancer and independently predicts pCR. HER2DX provides a reliable genomic tool that translates complex tumor biology into standardized scores, complements pathology, and supports personalized decision-making in HER2-positive breast cancer.