PS2-10-15. Prospective evaluation of a mRNA *ERBB2* score as a tool to guide HER2 status and accelerate neoadjuvant decision-making in ER-negative/low breast cancer

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Background

- In early-stage estrogen receptor (ER) negative breast cancer (BC), whether HER2-positive (HER2+) or triple negative (TNBC), neoadjuvant therapy is frequently employed, making diagnostic turnaround time a critical factor in treatment planning.
- The *ERBB2* mRNA score, developed and validated to predict HER2 status according to ASCO/CAP criteria, has demonstrated high accuracy (AUC=0.97; EBioMedicine 2022).
- HER2DX and TNBCDX assays, both of which incorporate this score, are performed using the same RNA-based platform, enabling rapid and integrated molecular profiling.
- However, whether this transcriptomic approach can outperform conventional HER2 immunohistochemistry/ in situ hybridization (IHC/ISH) testing in ER-negative tumors has not yet been prospectively evaluated.

Methods

- Patients with ER-negative early breast cancer (ER<10%) at the Breast Cancer Unit at the Clínic Barcelona Comprehensive Cancer Center were enrolled.
- RNA was extracted from formalin-fixed paraffin-embedded (FFPE) tumor tissue and analyzed using Reveal Genomics' RNA platform. Based on *ERBB2* mRNA expression levels, tumors classified as *ERBB2*-low received the TNBCDX Research Use Only (RUO) report, whereas those with medium or high *ERBB2* levels received the HER2DX report.
- All cases underwent parallel HER2 IHC and ISH testing (mean turnaround ~48h). In the prospective cohort, HER2 status was determined according to the updated 2025 ASCO/CAP guidelines, which introduced the HER2-ultralow (0+) category and refined scoring into a 5-tier system (0, 0+, 1+, 2+, 3+).
- Additionally, we explored the *ERBB2* score in 257 ER-negative tumors (93 HER2+ and 164 TNBC) from 4 cohorts (i.e., BIONHER, DAPHNe, ATEMPT and a combined TNBC Spanish cohort from Clínic Barcelona Comprehensive Cancer Center, and University Hospital 12 de Octubre).

Objective

To prospectively evaluate whether the *ERBB2* mRNA score can accurately predict HER2 IHC/ISH status in newly diagnosed ER-negative/low breast cancer. The primary endpoint was the concordance between the HER2DX *ERBB2* mRNA score and final HER2 status by IHC/ISH.

Results

- As of October 1st 2025, 45 patients with newly diagnosed ER-negative BC (11 HER2+ and 34 TNBC) have been enrolled (table 1).
- Concordance between the HER2DX *ERBB2* mRNA score and HER2 IHC/ISH status was 100%. Eleven cases (24.4%) were classified as *ERBB2* medium/high and received the HER2DX report, while 34 cases (75.6%) were *ERBB2* low and received the TNBCDX report (figure 1 and 2).
- The proportion of HER2+ tumors (i.e., IHC 3+ or IHC 2+ with ISH amplification) was consistent with the *ERBB2* medium/high group, whereas the *ERBB2*-low group was TNBC (i.e., IHC 0, 1+, 2+ without ISH amplification). ROC analysis showed excellent discrimination for HER2 positivity, AUC = 1.00.

Table 1. Baseline characteristics of the ER negative prospective cohort
SD: standard deviation. IQR: interquartile-range. pCR: pathologic complete response.
Percentages calculated over the total cohort (n=45).

Variable	Category	n (%)
ER status	ER 0	39 (86.7)
	ER-low (1–10%)	6 (13.3)
HER2 IHC score	0	8 (17.8)
	0+	11 (24.4)
	1	10 (22.2)
	2	8 (17.8)
	3	8 (17.8)
HER2 ISH status	Not amplified	5 (11.1)
	Amplified	3 (6.7)
HER2 final status	Negative	34 (75.6)
	Positive	11 (24.4)
pCR category	High pCR	18 (40.0)
	Low pCR	8 (17.8)
	Medium pCR	19 (42.2)
ERBB2 mRNA group	Low	34 (75.6)
	Medium/High	11 (24.4)
***ERBB2* mRNA score (0-100)**		
Mean (SD)		18.4 (26.9)
Median (IQR)		2.0[1.0-27.0]

- Finally, in the retrospective combined ER-negative cohort of 257 samples, the *ERBB2* score accurately predicted HER2 IHC/ISH status, with 95.3% concordance and an AUC of 0.99. Among the *ERBB2* medium/high group, 17 patients (15.7%) were classified as HER2-negative; whereas only 2 out of 149 (1.3%) in the *ERBB2* low group were categorized as positive (figure 3 and 4).
- Discordant *ERBB2*-IHC/ISH cases may warrant pathological review.

Figure 1. Distribution of HER2 IHC and ISH status across *ERBB2* mRNA groups in the prospective cohort

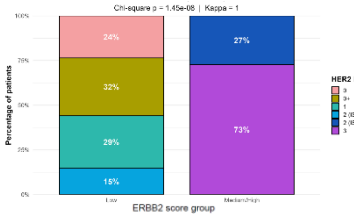


Figure 2. Boxplot of *ERBB2* mRNA levels according to HER2 status (IHC/ISH) in the prospective cohort. A strong positive correlation was observed between HER2 IHC/ISH category and *ERBB2* mRNA levels.

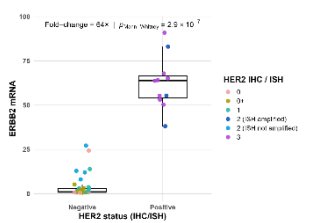


Figure 3. Distribution of HER2 IHC and ISH status across *ERBB2* mRNA groups in the retrospective cohort

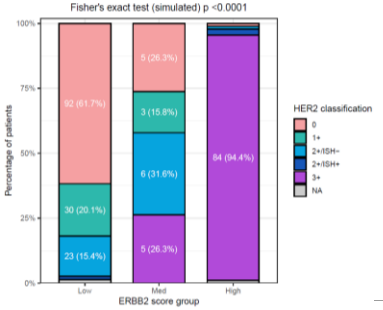
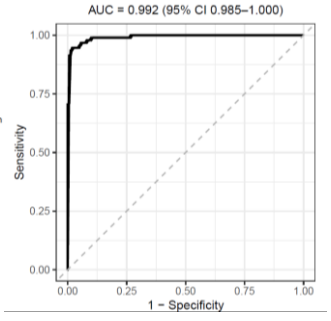


Figure 4. ROC curve for *ERBB2* mRNA vs HER2 IHC/ISH in the retrospective cohort



Conclusions

This ongoing pilot study demonstrates the feasibility of using an upfront *ERBB2* mRNA-based score to guide selection of HER2DX or TNBCDX testing in patients with newly diagnosed ER-negative breast cancer. Preliminary results show perfect concordance with standard HER2 IHC/ISH testing and support the potential of this approach as a practical tool in the neoadjuvant setting.

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