Editorial Commentary

The predictive value of HER2DX assay with pathological response and prognosis in patients with early HER2-positive breast cancers: commentary on the PHERGain trial

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Breast cancer (BC) is the most common type of cancer among women worldwide and the majority of patients are diagnosed at an early-stage (1). While neoadjuvant chemotherapy should be applied in all appropriate patients (2), the adverse events from chemotherapy may be greater than the potential benefit. Therefore, detecting patients who have potent clinically significant benefits from chemotherapy is critical. BC is a greatly heterogeneous disease. Each subtype, luminal A, luminal B, human epidermal growth factor receptor 2-positive (HER2$^+$), and triple-negative BC (TNBC), has distinctive molecular features and signal transduction (3). Previously, assessments to escalate or de-escalate BC chemotherapy mainly depended on traditional parameters, such as tumor size, pathological type, lymph node metastasis, hormone receptor (HR) status, tumor-infiltrating lymphocytes (TILs), and Ki-67 proliferation index. Especially among them, TILs can predict the usefulness of systematic therapy and prognosis for BC (4). Accumulating evidence suggests that screen detection provides an additional survival benefit beyond stage shift and also reduces the risk of systemic recurrence (5). Meanwhile, the role of molecular signatures in selecting patients who could be spared chemotherapy has been recognized as a high priority for translational BC research (6,7). Recent advancements in some genomic assays, such as OncotypeDX (Genomic Health, Redwood City, CA, USA), PREDICT Plus, and MammaPrint (Agendia, Irvine, CA, USA), have established the prospective role in making adjuvant treatment decisions and predicting prognoses for early-stage HR-positive/HER2-negative BC patients (8-10).

The HER2DX genomic test was initially designed particularly for HER2$^+$ BC and predicted pathological complete response (pCR) and survival outcomes in early-stage HER2$^+$ BC. This signature incorporates data concerning tumor size, nodal status, and 27 genes representing four gene expression signatures, which are associated with proliferation, tumor cell differentiation, immune infiltration, and HER2 amplicon. According to the clinical features, three scores were created by integrating genomic data: the HER2DX risk score (RS), the HER2DX pCR score, and the HER2DX Erb-B2 receptor tyrosine kinase 2 (ERBB2) expression score, which assists in predicting survival and the risks of relapse and metastasis in HER2$^+$ BC patients, leading to the guidance of treatment approaches. HER2DX is now being clinically applied as an

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option for patients with HER2$^+$ BC testing, which could possibly spare thousands of patients from chemotherapy-related disease. HER2DX has been assessed in multiple clinical trials (*Table 1*). As a result of these trials, HER2DX is currently widely used in clinical practice to guide personalized therapy and predict prognosis. However, it is not clear whether the risk of relapse score can be calibrated to provide a balance between the benefits and harms of chemotherapy that would be acceptable to patients. In this issue of *Clinical Cancer Research*, Llombart-Cussac and colleagues report a unique aspect of the PHERGain study (clinical trial registry: NCT03161353) (17). They aimed to ascertain if HER2DX RS can predict the pCR, defined as ypT0/is ypN0, in patients with newly diagnosed early-stage HER2$^+$ BC undergoing de-escalation neoadjuvant chemotherapy. For this purpose, the authors retrospectively analyzed randomized, open-label phase II study data obtained from formalin-fixed, paraffin-embedded core tumor biopsies of 356 patients with HER2$^+$ early BC, treated across 45 hospitals in seven European countries. The pCR rate was 56.4% in TCHP (docetaxel, carboplatin, trastuzumab, and pertuzumab) group and 33.8% in trastuzumab-pertuzumab (HP) ± endocrine therapy group. The overall pCR rate was 38.0%. Multivariate regression analysis, involving therapy and clinicopathologic factors, found that the HER2DX pCR score was potently relevant to pCR [odds ratio (OR), 1.29; 95% confidence interval (CI): 1.10–1.54; P<0.001]. HER2DX-defined pCR-high, med, and low groups by the HER2DX pCR score were subsequently examined to analyze these findings further. The pCR rates were 50.4%, 35.8%, and 23.2%, respectively (pCR-high *vs.* pCR-low: OR, 3.27; 95% CI: 1.54–7.09; P<0.001). Notably, in patients with relapse disease, 3-year invasive disease-free survival (iDFS) was 89.8% in the HER2DX high-risk group and 100% in the low-risk group [89.8% *vs.* 100%: hazard ratio (HR), 2.70; 95% CI: 0.60–12.18; P=0.197]. Patients with residual disease represented a potently lower iDFS than those achieving pCR (HR, 0.13; 95% CI: 0.02–0.98, P=0.048), helping to identify the prognostic impact of treatment efficacy. HER2DX predicts pCR in the setting of neoadjuvant HP-based therapy, independently of HR status, ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) response, and treatment modality, and might identify patients at higher risk of recurrence among patients with residual disease. Meanwhile, the correlation between HER2DX pCR score and prognostic RS was weak, because there is no significant difference between HER2DX high-risk and low-risk concerning a 3-year iDFS (89.8% and 100.0%, respectively; 95% CI: 0.6–12.2; P=0.197). HER2DX RS may aid in predicting optimal candidates for the de-escalation of neoadjuvant chemotherapy in early-stage HER2$^+$ BC patients.

With the caveats of the concerns noted by the authors (reliance on retrospective data, small sample size with limited statistical power and accuracy, short follow-up, and small number of events), a recent retrospective study found that the HER2DX RS was found to be significantly associated with long-term survival outcomes in patients with residual disease. At least with respect to the caveats and limitations recognized by the authors, this study provides valuable information about the potential clinical utility of the HER2DX assay in determining treatment strategies for early-stage HER2$^+$ BC and warrants potential identification. However, several other considerations may need to be regarding the usefulness of the HER2DX and the potential clinical benefit of anti-HER2 treatment. HER2DX assay predominantly evaluates the combination therapy of trastuzumab and pertuzumab. Nowadays, HER2-targeting therapy is rapidly evolving with the development of novel anti-HER2 agents, such as monoclonal antibodies [margetuximab, and ado-trastuzumab emtansine (ado-T-DM1)], small molecule tyrosine kinase inhibitors (pyrotinib, tucatinib, neratinib, and lapatinib), and antibody-drug conjugates [such as T-DM1, trastuzumab deruxtecan (T-DXd), and disitamab vedotin (RC-48)]. Nevertheless, in the PHERGain study, HER2DX overlooked the roles of these agents in dual-targeted therapy. Validating HER2DX in broader treatment regimens would be required. The work in HER2$^+$ BC represents progress, but this progress needs higher financial costs which lead to the restriction of extensive clinical usage. Thus, it is important to reduce costs and economic burdens. A multicenter, prospective, randomized, open-label, phase III study DEFINITIVE trial (clinical trial registry: NCT06446882) proposes to evaluate the health-related quality of life (HRQoL), safety, efficacy, and financial costs in patients who had newly diagnosed stage II to IIIA HER2$^+$ BC that was treated with neoadjuvant therapy by using HER2DX assay. This study aims to ascertain the superiority of HRQoL using the Gastrointestinal Health Scale (GHS) and the score from the FACIT Fatigue Scale. Economic evaluation to assess cost-effectiveness will be examined using the EuroQol-5D-5L questionnaire for health economic analysis. The results of this trial may support decision-making for patients with early-stage HER2$^+$ BC in using HER2DX

Table 1 Summary of clinical trials related to HER2DX

Trial	Clinical trials number	Intervention	Phase	Patient population	Rate of pCR	Molecular typing	Ref.
CALGB-40601	NCT00770809	Paclitaxel + trastuzumab + lapatinib or paclitaxel + trastuzumab or paclitaxel + lapatinib	III	305	THP: 56%, 95% CI: 47–65%; TH: 46%, 95% CI: 37–55%; TL: 32%, 95% CI: 22–45%	HER2$^+$	(11)
ISPY-2	NCT01042379	T-DM1 + pertuzumab or paclitaxel + trastuzumab + pertuzumab, or a control arm of paclitaxel + trastuzumab. Doxorubicin + cyclophosphamide before surgery	II	128	T-DM1/P: 55%, 95% PI: 41–69%; THP: 56%, 95% PI: 42–70%; TH: 25%, 95% PI: 11–38%	HER2$^+$	(11,12)
PAMELA	NCT01973660	Trastuzumab + lapatinib ± letrozole or tamoxifen	II	151	41%, 95% CI: 31–51%	HER2$^+$	(13)
PerELISA	NCT02411344	–	–	–	–	HER2$^+$	(14)
DAPHNe	NCT03716180	Paclitaxel + trastuzumab + pertuzumab before surgery	II	98	56.7%	HER2$^+$	(15)
BiOnHER	NCT05912062	Trastuzumab + pertuzumab without chemotherapy followed by + trastuzumab + pertuzumab	II	49	45.6%	HER2$^+$	(11)
NEOHER	–	Docetaxel + pertuzumab + trastuzumab ± carboplatin	–	44	THP: 66.7%; THCP: 78.6%	HER2$^+$	(16)
GOM	–	Docetaxel + carboplatin + trastuzumab ± pertuzumab	–	155	TCH: 57%, 95% CI: 49–65%; TCHP: 61%, 95% CI: 50–71%	HER2	(11,12)
PHERGain	NCT03161353	Trastuzumab + pertuzumab± endocrine therapy docetaxel + pertuzumab + trastuzumab + carboplatin	II	356	TCHP: 56.4%; HP: 33.8%	HER2$^+$	(17)

CI, confidence interval; HER2$^+$, human epidermal growth factor receptor 2-positive; P, pertuzumab; pCR, pathological complete response; PI, probability interval; ref., reference; TCH, docetaxel, carboplatin, and trastuzumab; TCHP, docetaxel, carboplatin, trastuzumab, and pertuzumab; TH, docetaxel-trastuzumab; THP, docetaxel, trastuzumab, and pertuzumab; TL, docetaxel-lobaplatin; T-DM1, trastuzumab emtansine.

more effectively. Another problem is the lack of description regarding drug resistance. The HER2DX model could also help predict drug resistance in addition to pCR and prognostic outcomes. The association between drug resistance and reduced pCR rates may indicate HER2DX's potential in predicting resistance. Future research into the genes within the HER2DX assay and their roles in resistance mechanisms could provide strategies to overcome resistance. Meanwhile, growing evidence has demonstrated a prognostic role of TILs in HER2$^+$ cancers (4). TIL is correlated with better outcome and a higher possibility of obtaining a pCR response. Thus, considering that TIL is involved in HER2DX signature, it may be useful to clarify the prognostic association between pCR and TIL.

In conclusion, the work by Llombart-Cussac and colleagues established the prediction value of HER2DX with pCR and iDFS in patients with early HER2$^+$ BC patients preoperatively treated with TCHP and HP, as further development of the HER2DX assay. This is likely to become the tool for enabling more accurate treatment decisions and predictions of survival as well as the risk of recurrence and metastasis, which allows clinicians to tailor treatment and monitoring to the individual patient. Further clinical trials evaluating the predictive value of other novel anti-HER2 agents, cost-effectiveness, and drug resistance are necessary for clinical practice.

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