In Silico Evaluation of the 12-Gene Molecular Score (EndoPredict) and the Recurrence Score (Oncotype DX) as Predictors of Response to Neo-adjuvant Chemotherapy in Estrogen Receptor Positive, HER2 Negative Breast Cancer

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BACKGROUND

- Neo-adjuvant chemotherapy (NaCT) facilitates complete surgical resection in locally advanced, estrogen receptor positive (ER+), HER2 negative (HER2-) breast cancer.
- In contrast to HER2+ and triple negative (TN) disease, pathologic complete response in ER+, HER2- breast cancer is rare (7-10%), leading to overtreatment in the absence of further stratification.
- Markers predictive of response would facilitate more individualized application of NaCT.
- The 12-gene molecular score (EndoPredict) and the 21-gene recurrence score (Oncotype DX) are validated prognostic markers in ER+, HER2- negative breast cancer.
- Here we use microarray-based expression data to evaluate the ability of these scores to predict NaCT response in ER+, HER2- breast cancer and improve identification of patients likely to benefit from the addition of chemotherapy versus endocrine neoadjuvant therapy alone.

METHODS

COHORT

- Public microarray RNA expression data and clinical variables were obtained from GEO data sets of breast cancer patients who received neo-adjuvant chemotherapy and had pre-treatment biopsies and pathological response data (GSE entries 16716, 20271, 25066, 32646, 34138, 41998).
- ER+, HER2- samples were selected based on provided immunohistochemistry data.

STATISTICAL ANALYSIS

- The 12-gene molecular score and 21-gene recurrence score were approximated according to published algorithms using expression means of array probes corresponding to the respective genes.
  - Probes were present for all genes except MYBL2 in GSE34138.
  - Scores were centered by the mean and scaled by standard deviation within each cohort.
- Association of the expression scores with pathologic complete response (pCR) was tested by logistic regression with adjustment for cohort.

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RESULTS

- Across the six data sets, 764 patients had ER+, HER2- disease by immunohistochemistry, 59 of whom experienced pCR, for a response rate of 8% (Table 1).
- The 12-gene molecular score and the 21-gene recurrence score were moderately well correlated (r^2=0.71) (Figure 1).

Figure 1. Correlation between expression scores by cohort

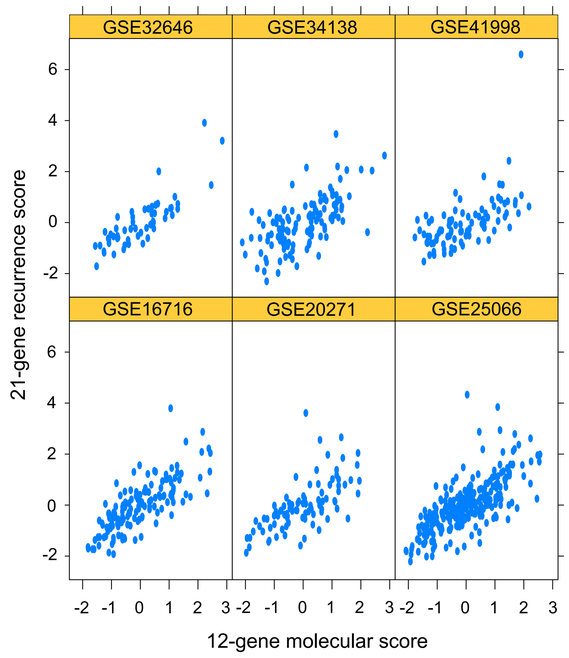


Table 1. GEO data sets included in analysis

GEO Data Set	ER+, HER2- (N)	Responders (N)
GSE16716	140	7
GSE20271	89	6
GSE25066	268	27
GSE32646	55	5
GSE34138	119	4
GSE41998	93	10
Combined cohorts	764	59

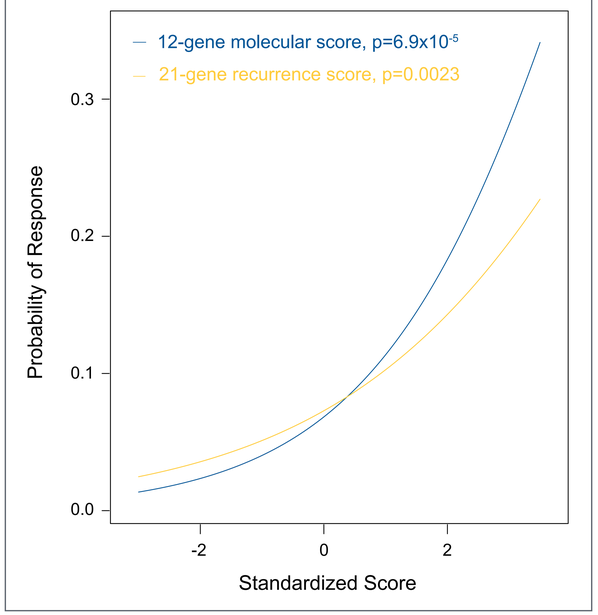
- Both expression scores were predictive of pCR, with higher scores indicating improved response rates (Table 2).
- In bivariate analysis, the 12-gene molecular score remained a significant predictor of response while the 21-gene recurrence score did not (Table 2, Figure 2).

Table 2. Association of expression scores with pathologic complete response by logistic regression adjusted for cohort

Analysis / Marker	OR (95% CI)	p-value
Univariate Analysis		
12-gene molecular score	1.039 (1.020, 1.059)	$6.9x10^{-5}$
21-gene recurrence score	1.030 (1.011, 1.049)	0.0023
Bivariate Analysis		
12-gene molecular score	1.036 (1.008, 1.063)	0.01
21-gene recurrence score	1.005 (0.978, 1.032)	0.73

OR, Odds Ratio; CI, Confidence Interval

Figure 2. Predicted probability of pathologic complete response by expression score



CONCLUSIONS

- In this microarray-based analysis, the 12-gene molecular score was highly predictive of ER+, HER2- complete response to NaCT.
- Optimal stratification of patients with ER+, HER2- breast cancer for NaCT offers the opportunity to individualize care, improve response rates, and possibly avoid ineffective treatment.