Editorial: Gene Expression Profile Assays As an Aid in Treatment Decision Making in Early-Stage Breast Cancer

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Each year, more than 200,000 women in the United States are diagnosed with invasive breast cancer, and approximately 40,000 die from the disease.¹ Nearly half of these women present with hormone receptor–positive, lymph node–negative disease, a subgroup that has increased in size due largely to routine breast cancer screening and

increased awareness. Currently, the decision to treat early-stage breast cancer with adjuvant chemotherapy and hormonal therapy is based on clinical and histologic criteria including tumor size, grade, hormone receptor status, human epidermal growth factor receptor (HER-2)/*neu* overexpression, and the presence or absence of lymph node involvement. Patient menopausal status may affect treatment decisions due to presumed lower recurrence risk and both smaller benefit and greater toxicity with systemic chemotherapy in older women. Clinical practice guidelines recommend adjuvant chemotherapy as well as hormonal therapy for most women with hormone receptor–positive, lymph node–negative early-stage breast cancer. However, the majority of women with hormone receptor–positive lymph node–negative breast cancer do not develop distant recurrence or death even in the absence of adjuvant chemotherapy. In addition, systemic chemotherapy is associated with both immediate and delayed toxicity, as well as considerable cost.^{2,3} At the same time, randomized controlled trials have shown that adjuvant chemotherapy is beneficial in some women with early-stage breast cancer, while others will develop distant metastases despite receiving chemotherapy.⁴ Many breast cancer patients therefore continue to be either overtreated or undertreated with adjuvant chemotherapy due to the lack of sufficiently accurate prognostic and predictive information. The availability of high-performance screening techniques using DNA microarrays has permitted analysis of gene expression patterns and study of their relationship to the risk of disease recurrence as well as treatment effectiveness, in an effort to guide clinicians in their daily decisions on the use of systemic adjuvant therapy.

As discussed in the article by Oratz et al in this issue of *Journal of Oncology Practice*,⁵ a gene expression profile assay has been developed based on reverse-transcriptase polymerase chain reaction (RT-PCR) methods applied to fixed paraffin-embedded tissue.⁶ From 250 cancer-related candidate genes gathered from microarray data and genomic databases, a 21-gene expression signature was found to provide good RT-PCR performance and accurate risk prediction. A recurrence score (RS; Oncotype DX; Genomic Health Inc, Redwood City, CA) ranging from 0 to 100 was derived from each patient's gene expression results using

a proprietary formula.⁷ Patients were categorized into low- (< 18), intermediate- (18 to 30), and high-risk (≥ 31) groups. This assay was independently validated as a prognostic indicator of distant recurrence-free survival in 668 assessable patients in node-negative, receptor-positive breast cancer treated with tamoxifen in the National Surgical Adjuvant Breast Program (NSABP) B-14 study.⁸ In a cost-utility analysis based on this initial validation study using a Markov model, the assay was found to be cost saving in more than two thirds of simulations.⁹ Subsequently, the accuracy of the 21-gene signature has been validated in terms of predicting the response to either chemotherapy and/or hormonal therapy among 651 patients on NSABP B-20 and 645 patients on NSABP B-14.¹⁰ A recent economic analysis incorporating the results from both of these validation studies demonstrated that treatments guided by the results of the RS assay could provide a net cost savings compared with routine chemotherapy, and an incremental cost-effectiveness ratio of approximately \$1,300 per life-year saved compared with tamoxifen alone.¹¹

These studies suggest that treatment decisions based on the results of gene expression assays can be efficacious, safe, and either cost-effective or actually cost-saving in selected women with early-stage breast cancer. Nevertheless, many questions remain, and further evaluation of the clinical utility of gene expression profile signatures to estimate disease prognosis and to predict treatment response in women with breast cancer are needed.^{12,13} The use of these assays in therapeutic decision-making must consider both the limitations of assay performance and the specific patient population being evaluated. The results of a meta-analysis of test performance characteristics of gene expression profile assays in estimating the risk of disease recurrence in women with early-stage breast cancer was recently reported.¹⁴ Unlike the extensive validation of the 21-gene expression assay noted here, many of the validation studies included were small or had limited patient follow-up for recurrence. Study-reported assay accuracy and discrimination varied considerably with false-positive and false-negative rates, with ranges of 0% to 33% and 6% to 67%, respectively. Sources of variation across studies included differences in study population and clinical setting, inconsistent reporting of patient characteristics, as well as assay characteristics including the cut-points utilized. As expected, the predictive value of the gene signatures depends on not only the sensitivity and specificity of the assay but also on the a priori risk of distant recurrence in the population under study.¹⁴ Perhaps one of the most intriguing observations needing further exploration was the observation that the number of genes in the assay correlated significantly with the prognostic accuracy of the assay.

Clearly, the greatest challenge ahead is to define the appropriate role of these assays in clinical practice and treatment decision making. The study by Oratz et al,

demonstrates that the results of the assay may alter treatment in upwards of a quarter of eligible patients, with the greatest effect resulting in a decision not to use chemotherapy if low or intermediate RSs are reported.⁵ Particularly problematic is the choice of treatment in patients with intermediate-risk RSs. The results from the previous validation studies left some uncertainty with regard to the relative efficacy of chemotherapy in this population.^{7,10} There are also very little data on the accuracy of the assay when applied to women with breast cancer treated with either an aromatase inhibitor or modern anthracycline- or taxane-based chemotherapy. As a result, the Breast Cancer Intergroup has initiated the Program for the Assessment of Clinical Cancer Tests (PACCT-1), and the Trial Assigning Individualized Options for Treatment, or the TAILORx Trial, also available through the Cancer Trials Support Unit (CTSU) of the National Cancer Institute. Women aged 18 to 75 years with hormone receptor–positive, HER-2–negative, lymph node–negative, early-stage breast cancer, with tumors less than 5 cm in size, are eligible. After obtaining informed consent, the patient's tumor sample is submitted for the *Oncotype DX* Assay. Patients with resulting RSs less than 11 (low risk) or more than 25 (high risk) will be assigned to hormonal therapy alone or chemotherapy and hormonal therapy, respectively (Fig 1). Patients with an RS of 11 to 25 will be randomly assigned to hormonal therapy alone or chemotherapy and hormonal therapy following stratification on the basis of tumor size, menopausal status, type of chemotherapy, and planned radiation therapy. Upwards of 10,000 patients will be registered and monitored for disease recurrence or death. It is anticipated that the results of this study will not only further validate the accuracy of the gene assay but will also further clarify the utility and value of this assay in the management of women with early-stage breast cancer. Questions will remain, but this trial should take us an additional step toward integrating such approaches into clinical decision making in oncology, and individualizing the treatment of women with breast cancer

Figure 1. Breast Cancer Intergroup Program for the Assessment of Clinical Cancer Tests (PACCT-1); Trial Assigning Individualized Options for Treatment or the TAILORx Trial. RS, recurrence score based on 21-gene assay; ER/PR+, estrogen or progesterone receptor–positive.

who are at greatest risk and who are most likely to benefit from available treatments.

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Authors' Disclosure of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict existed for drugs or devices used in a study if they are not being evaluated as part of the investigation.

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