Impact of a Commercial Reference Laboratory Test Recurrence Score on Decision Making in Early-Stage Breast Cancer

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Abstract

Purpose: To investigate whether recurrence score (RS) as determined using a commercial reference laboratory test influences clinicians' treatment recommendations and eventual treatment in patients with early-stage breast cancer.

Methods: A retrospective analysis was performed on 74 patients from a community-based oncology practice with estrogen receptor (ER) –positive, lymph node (LN) –negative stage I or II breast cancer for which RS was obtained. Demographic and pathology information was extracted from medical records. Ten-year relapse-free survival was calculated using Adjuvant! Online. Treatment recommendations before the RS knowledge were compared with treatment recommendations after RS knowledge and to the treatment eventually administered.

Results and Conclusion: A weak correlation was found between RS and both patient age and tumor size, modest correlation between RS and tumor grade, and modest correlation

between RS and 10-year recurrence as determined by Adjuvant! Online. For 21% and 25% of patients, knowledge of the RS changed the clinicians' treatment recommendations and eventual treatment, respectively. The decision to change from hormone therapy to chemotherapy (with or without hormone therapy) was generally associated with high RS (high distant recurrence risk as determined by the commercial reference laboratory test), whereas the decision to change from chemotherapy to hormone therapy was generally associated with low RS (low distant recurrence risk as determined by the commercial reference laboratory test). Knowledge of the RS changed treatment recommendations and eventual treatment in patients with ER-positive/LN-negative early-stage breast cancer. Use of genomic-based prognosis may result in more accurate estimates of true recurrence risk than currently possible with commonly used prognostic factors (such as patient age, tumor size, and tumor grade) alone and thus lead to an increase in appropriate adjuvant therapy decision making.

Introduction

One of the most complex decisions faced by an oncologist involves the use of adjuvant treatment in early-stage breast cancer. In these instances, the oncologist must consider the patient's risk of recurrence, the benefits and toxicity of any proposed therapy, and the patient's input in the decision-making process.

Traditionally, oncologists have used certain risk factors to help gauge the risk of recurrence of early-stage breast cancer. These factors include tumor size, hormone receptor status, and tumor grade.[1] The Onco*type* DX breast cancer assay (Genomic Health Inc, Redwood City, CA) has been validated as an independent prognostic measure of the risk of recurrence for women with estrogen receptor–positive and lymph node–negative breast cancer.[2] By calculating a recurrence score (RS) based on the expression of 21 genes, the Onco*type* DX assay gives a quantitative risk of distant recurrence of breast cancer at 10 years when patients are treated with systemic tamoxifen alone. This risk estimate has been shown to be independent of and superior to patient age, tumor size, and tumor grade as a prognostic factor for breast cancer recurrence in this subgroup of women.[2]

This study was designed to see how the RS influences the adjuvant treatment recommendations in a busy oncology practice. The primary purpose of this study was to investigate whether the availability of the RS changed practice patterns and specifically to explore whether the availability of the RS was associated with a change in adjuvant treatment recommendations originally made on the basis of commonly-used prognostic factors and whether the availability

of the RS was associated with a difference in actual treatment received compared with the original recommendations.

The secondary purposes of the study were to assess the correlation of the RS with the patient's age and with tumor size and tumor grade and to assess the correlation of the risk of recurrence predicted by the RS with that predicted by Adjuvant! Online (www.adjuvantonline.com), a popular tool based on the standard measures that are commonly used by oncologists to assess recurrence risk.

Methods

Study Design

Rocky Mountain Cancer Centers is headquartered in Denver, Colorado. It comprises a large, private practice oncology group, part of the US Oncology Network. All four oncologists from that group participated in this study. Seventy-four consecutive breast cancer patients with estrogen receptor–positive, lymph node–negative disease for whom the Onco*type* DX assay was ordered were selected for the study. These patients spanned a time period from January 2004 through April 2005. There were no set criteria for ordering the Onco*type* DX assay; each oncologist ordered the test when he/she felt it was clinically appropriate. All patients for whom the assay was ordered during that time period were included in this analysis. The assays were ordered through the normal commercial process from the Genomic Health reference laboratory in Redwood City, California. RS was determined by using this assay on tumor tissue from 72 of these patients (two patients [3%] had insufficient

tumor to allow RS determination). Demographic information and pathology data were obtained from the medical records for all of these patients. In particular, patient age, tumor size, and tumor grade were noted.

The medical records were also examined to determine the original adjuvant treatment recommendation made before knowledge of the RS and the adjuvant treatment actually received by the patient. The original treatment recommendation had not been recorded for four patients, which left 68 patients for this study.

Relevant clinical information extracted from the medical record was also entered into the Adjuvant! Online program for these 68 patients. This Internet program generates a 10-year risk of disease recurrence (distant and local) based on large databases of information.

Statistical Analysis

Statistical analyses were performed according to a predefined statistical analysis plan. A descriptive analysis was performed to stratify patients according to initial treatment recommendation (before knowledge of the RS), after RS treatment recommendation, and actual treatment administered (hormone therapy alone [HT] or chemotherapy ± HT [CT]). These groups were further analyzed according to predefined RS risk categories (low, < 18; intermediate, 18 to 30; high, ≥ 31).

Analysis of variance was used to evaluate the association between RS and tumor grade. The Tukey-Kramer method for pairwise comparisons was used to test the statistical significance of differences between the mean RS for each tumor grade while maintaining the overall type I error rate at .05.[3] Correlation analyses were utilized to determine the association between the RS and patient age, tumor size, and the risk of 10-year distant recurrence as determined by Adjuvant! Online.

The influence of the RS on the final treatment recommendation was investigated by comparing the treatment recommendation made in the absence of the RS to the treatment recommendation after knowledge of the RS. The odds ratio was used to compare the likelihood of a change in the treatment recommendation given a low versus a high RS. The same approach was used to evaluate the influence of the RS on the treatment actually administered. Exact inference methods were used for significance testing of the odds ratio.[4]

Results

Demographics

The demographic information for 68 patients can be found in Table 1. It is interesting to note that 32 (47%) of 68 patients had tumors ≤ 1 cm in size. Because these patients were drawn from a consecutive series of breast cancer patients, this may reflect the large number of small tumors seen in clinical practice.

Table 2 lists the distribution of RS obtained for the 68 patients in this study. This distribution is similar to that obtained in the validation study of Onco*type* DX involving 668 patients, where a distribution RS showed that 51% of patients were low risk

Table 1. Patient Demographics and Baseline Characteristics

Characteristic	No.	%
Sex		
Male	1	
Female	67	
Age, years		
Median	54	
Range	35-77	
Tumor type		
Infiltrating ductal carcinoma	55	81
Infiltrating lobular carcinoma	4	6
Mucinous carcinoma	4	6
Tubular carcinoma	1	1.5
Mixed	3	4
Missing	1	1.5
Tumor size, cm		
Mean	1.2	
SD	0.6	
Tumor size distribution, cm		
0-1	32	47
1.1-2.0	28	41
2.1-3.0	8	12
Tumor grade distribution		
I	30	44
II	24	35
III	14	21

(RS, < 18), 22% were intermediate risk (RS, 18 to 30), and 27% were high risk (RS, ≥ 31). [2]
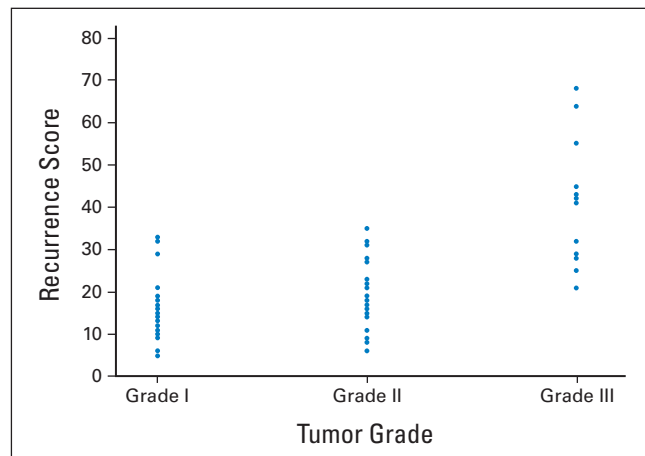
Correlation Between RS and Tumor Grade, Tumor Size, Patient Age, and Risk As Determined by Adjuvant! Online

The mean (standard deviation) RSs for grades 1, 2, and 3 tumors were 15.5 (6.8), 19.0 (8.0), and 40.4 (14.3), respectively. A statistically significant difference (95% CI) was found between grade 1 and 3 means (−24.8; −32.0 to −17.9) and between grade 2 and 3 means (−1.4; −28.8 to −14.0) but not

Table 2. Recurrence Score Distribution

Risk Group	No.	%
Total		
Mean	22	
Range	5-68	
Low risk	32	47
Intermediate risk	22	32
High risk	14	21

Figure 1. Correlation between recurrence score and tumor grade.

Figure 2. Correlation between recurrence score and patient age.

between grade 1 and 2 means (-3.4; -9.44 to 2.64). Figure 1 presents the scatterplot of RS by tumor grade.

A series of analyses was performed to examine the correlation of the RS generated for these 68 patients with patient age, tumor size, and the risk of 10-year recurrence as determined by Adjuvant! Online. A weak correlation was found between RS and both patient age (Fig 2; $R^2 = 0.04$; 95% CI, 0.00 to 0.17; $P < .01$) and tumor size (Fig 3; $R^2 = 0.07$; 95% CI, 0.00 to 0.22; $P = .03$). The correlation between the risk of distant recurrence at 10 years as estimated from the RS and the risk of overall recurrence (distant or local) at 10 years as estimated from Adjuvant! Online was modest (Fig 4; $R^2 = 0.43$; 95% CI, 0.24 to 0.59; $P < .01$).

RS and Treatment

The effect of the RS on adjuvant treatment recommendations is presented in Table 3. Among the 68 patients, the treating oncologist changed the adjuvant treatment recommendation in 14 (20%) after knowledge of the RS became available. In seven (50%) of these 14 patients, the recommendation was changed from HT to CT; in the remaining seven (50%), it was changed from CT to HT. In patients for whom the recommendation was changed from HT to CT, six (83%) of seven had an intermediate or high RS. The odds of the physician treatment recommendation changing from HT to CT were significantly higher ($P = .0011$) if the RS was high (odds ratio, 4:0) versus low (odds ratio, 1:18). There were no patients for whom an initial recommendation for HT was maintained after knowledge that the RS was high. In patients for whom the recommendation was changed from CT to HT, six (83%) of seven had a low RS. The odds of the physician treatment recommendation changing from CT to HT were significantly higher ($P = .0340$) if the RS was low (odds ratio, 6:7) versus high (odds ratio, 0:10). For patients with a high RS, there were no patients for whom an initial recommendation for CT changed to a recommendation for HT.

Comparison of before RS adjuvant recommendations with actual treatment received are presented in Table 4. Of 68 patients, 17 (25%) received a different adjuvant treatment (HT v CT) from that recommended before knowledge of the RS. For three patients
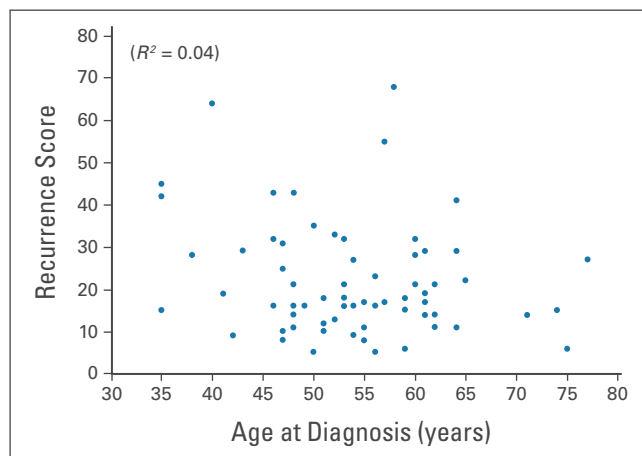
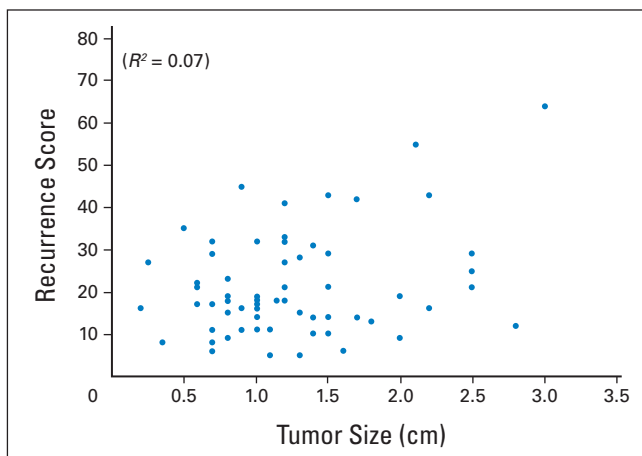**Figure 3. Correlation between recurrence score and tumor size.**

Figure 4. Correlation between 10-year distant recurrence as determined by the recurrence score (RS) and 10-year recurrence as determined by Adjuvant! Online.
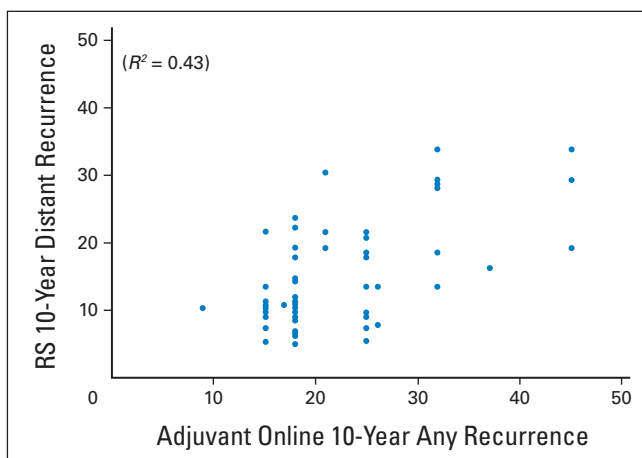
Table 3. Physician Treatment Recommendations Before and After RS Knowledge

Treatment Recommendation Before RS Knowledge	Treatment Recommendation After RS Knowledge	RS (No.)			Total	
		Low	Intermediate	High	No.	%
HT	HT	18	10	0	28	41
HT	CT	1	2	4	7	10
CT	HT	6	1	0	7	10
CT	CT	7	9	10	26	38

Abbreviations: RS, recurrence score; HT, hormone therapy; CT, chemotherapy with or without hormone therapy.

who eventually received CT, the original recommendation was HT. Two (67%) of these three patients had a high RS. The odds of CT treatment, given an initial physician treatment recommendation for HT, were significantly higher ($P = .0474$) if the RS was high (odds ratio, 2:2) versus low (odds ratio, 0:19). In 14 patients who eventually received HT, the original recommendation was CT. Nine (64%) of these 14 patients had a low RS. The odds of HT treatment, given an initial physician treatment recommendation for CT, were 20.3 times higher ($P = .0130$) if the RS was low (odds ratio, 9:4) versus high (odds ratio, 1:9).

Discussion

The Onco*type* DX assay is the first commercially available genomic test to help clinicians and patients determine the risk of distant recurrence in early-stage breast cancer. The assay is a validated prognostic test that assesses the risk of recurrence of a particular breast cancer based on a genomic expression profile.[2,5] Physicians have tried to estimate recurrence risk, which is essential for an adequate and appropriate adjuvant treatment decision, through the use of commonly used factors, such as patient age, hormone receptor status, tumor size, and tumor grade. This approach is problematic, however, given the lack of a uniform weighting of these elements and the poor correlation of tumor grading among various pathologists.[6] Adjuvant! Online represents an attempt to objectify a recurrence risk using these variables.

The demographic data regarding these consecutive patients is worthy of comment. These results are similar to those found in the major validation study of Onco*type* DX.[2] Specifically, almost one half (47%) of the RS values were in the low risk group, compared with slightly more than one half (51%) in the major validation study. The major difference was tumor size distribution. In the main validation study (in which tumor samples

were derived from the original National Surgical Adjuvant Breast and Bowel Project B-14 study and were therefore collected more than 15 years ago), 414 (62%) of 668 patients had a tumor ≤ 2.0 cm, whereas in this study, 60 (88%) of 68 patients had a tumor ≤ 2.0 cm. This higher percentage of smaller tumors in this study could reflect a nationwide trend toward smaller tumors at diagnosis, or reflect practice patterns for selecting patients for the test. In addition, the fact that the Onco*type* DX assay was ordered in a patient population with tumors ≤ 1 cm is consistent with the fact that the 10-year distant recurrence rate in T1a and T1b tumors is not negligible; not all of these patients do well.[7]

This retrospective view from a large community practice demonstrates that knowledge of the RS changed both the recommended adjuvant treatment and the actual treatment received compared with the initial adjuvant treatment recommendation made before the RS was available. In 21% of patients (14 of 68), knowledge of the RS changed the physician's treatment recommendation. An important finding is that the direction of the change was consistent with information provided by the RS. The odds of the physician's treatment recommendation changing from HT to CT were significantly higher (estimated as infinitely higher) if the RS was high versus low risk. The odds of the physician's treatment recommendation changing from CT to HT were significantly higher (estimated as infinitely higher) if the RS was low versus high risk. Thus, knowledge of the RS was associated with a statistically significant change in the adjuvant treatment recommendation consistent with the recurrence risk suggested by the RS.

In this study, recommendation changes were equally divided between CT to HT and HT to CT. This could have been due to the small sample size in this study. In larger data sets, approxi-

Table 4. Physician Treatment Recommendations Before RS Knowledge and Actual Adjuvant Treatment Administered

Treatment Recommendation Before RS Knowledge	Treatment Administered After RS Knowledge	RS (No.)			Total	
		Low	Intermediate	High	No.	%
HT	HT	19	11	2	32	47
HT	CT	0	1	2	3	4
CT	HT	9	4	1	14	21
CT	CT	4	6	9	19	28

Abbreviations: RS, recurrence score; HT, hormone therapy; CT, chemotherapy with or without hormone therapy.

mately 50% of patients had a low RS and 25% of patients had a high RS.[2] Hornberger et al[8] demonstrated that, given current treatment recommendations and the expected distribution of RS, the change in treatment recommendations after RS knowledge is expected to be more from CT to HT than from HT to CT. It should also be mentioned that each oncologist ordered the Onco*type* DX assay per his/her clinical ordering patterns as opposed to a rigid criteria. Thus, the choice of patients for whom the test was ordered could have influenced the distribution of recommendations.

In 25% of patients (17 of 68), knowledge of the RS changed the actual treatment received compared with the pre-RS recommendation. Even though the direction of treatment recommendation change was evenly divided between CT to HT and HT to CT, the great majority of changes in actual treatment (14 of 17 patients; 82%) were from CT to HT and only a few (three of 17 patients; 18%) were from HT to CT. This discrepancy can be at least partially explained by the role of the patient in the decision-making process, which was not specifically examined in this study. For example, it is possible that a physician recommendation to change treatment from CT to HT would be more often accepted by a patient than a recommendation to change treatment from HT to CT. The role of the patient in the decision-making process warrants further study.

In situations where the recommendation or eventual treatment was not changed after RS knowledge was obtained, physicians and patients reported anecdotally that the RS provided increased confidence and reassurance that the treatment plan was appropriate. This result could potentially translate to increased patient compliance with the treatment plan. Future studies looking specifically at the patient component of decision making utilizing the RS are planned.

This study demonstrated only a poor correlation between the RS and both patient age and tumor size and a modest correlation between RS and tumor grade. These results are consistent with the main validation study of the Onco*type* DX assay where patient age and tumor size, but not poor tumor grade lost their predictive power of distant recurrence when the multivariate analysis included the RS.[2]

The value of the Onco*type* DX assay is, in part, that it provides an objectively measured risk of recurrence that is independent from the traditional factors. Adjuvant! Online is a practical tool that incorporates these traditional factors to yield a risk of recurrence. The risk of 10-year distant recurrence generated from the RS and the risk of recurrence generated from Adjuvant! Online were only modestly correlated, suggesting that the RS provides information not contained in Adjuvant! Online. Part of this difference may be explained by noting that Adjuvant! Online generates a risk that includes both distant and local recurrence, whereas the risk generated from the RS is only for distant recurrence. However, Bryant et al[9] demonstrated that the RS information regarding the risk of distant recurrence is independent from and superior to that provided by Adjuvant! Online.

Recently, Paik et al[10] demonstrated that the RS correlates not just with risk of distant recurrence at 10 years but also with chemotherapy benefit. The great majority of benefit from adjuvant chemotherapy in the National Surgical Adjuvant Breast and Bowel Project B-20 study was found in patients with a high RS, whereas those with a low RS had minimal if any benefit from adjuvant chemotherapy.[9] Thus, by identifying patients with a high (or low) risk of recurrence, the clinician is also identifying patients with a significant (or minimal) chemotherapy benefit.

In summary, this study demonstrates that knowledge of RS does indeed result in a change in clinical practice, both in treatment recommendations and actual adjuvant therapy received. Compared with the commonly used prognostic factors alone, knowledge of the RS can facilitate better alignment of patient recurrence risk with adjuvant treatment, which is the oncologist's goal in making adjuvant treatment decisions.

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

By Gary H. Lyman, MD, MPH

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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; Onco*type* 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 inhibitior 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 Onco*type* 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.
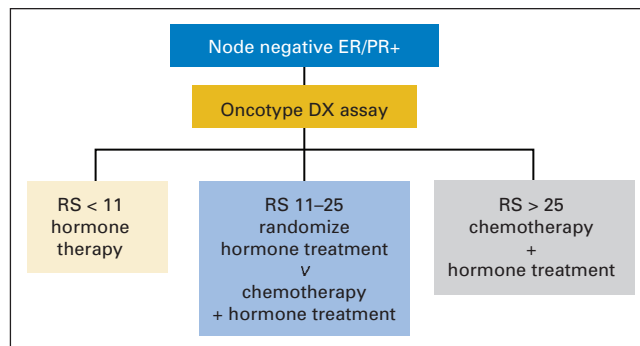
who are at greatest risk and who are most likely to benefit from available treatments.

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