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Review

Case-Based Review and Clinical Guidance on the Use of Genomic Assays for Early-Stage Breast Cancer: Breast Cancer Therapy Expert Group (BCTEG)

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Abstract

In addition to classical clinicopathologic factors, such as hormone receptor positivity, human epidermal growth factor receptor 2 (HER2) status, and tumor size, grade, and lymph node status, a number of commercially available genomic tests may be used to help inform treatment decisions for early breast cancer patients. Although these tests improve our understanding of breast cancer and help to individualize treatment decisions, clinicians face challenges when deciding on the most appropriate test to order, and the advantages, if any, of one test over another. The Breast Cancer Therapy Expert Group (BCTEG) recently convened a roundtable meeting to discuss issues surrounding the use of genomic testing in early breast cancer, with the goal of providing practical guidance on the use of these tests by the community oncologist, for whom breast cancer may be only one of many tumor types they treat. The group recognizes that genomic testing can provide important prognostic (eg, risk for recurrence), and in some cases predictive, information (eg, benefit of chemotherapy, or extended adjuvant endocrine therapy), which can be used to help guide treatment decisions in breast cancer. The available tests differ in the types of information they provide, and in the patient populations and clinical trials that were conducted to validate them. We summarize the discussion of the BCTEG on this topic, and we also consider several patient cases and clinical scenarios in which genomic testing may, or may not, be useful to guide treatment decisions for the practicing community oncologist.

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Introduction

The treatment of early breast cancer (EBC) is guided by well-established clinicopathologic factors, such as tumor size, grade, and lymph node (LN) status, as well as biomarkers such as estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2). These biomarkers dictate the use of therapies such as adjuvant endocrine therapy (ET; in the case of hormone receptor positivity), and/or anti—HER2-directed therapies such as trastuzumab, pertuzumab, trastuzumab emtansine, or neratinib (in the case of HER2 overexpression/amplification).

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Clinicopathologic factors are also important to help determine the natural history of breast cancer over time and the risk for disease recurrence; as such, they are essential for the clinician to establish, early in the course of disease, an overall risk assessment, which can dictate the need for risk-reducing strategies such as adjuvant chemotherapy.

Over the last decade, with ongoing advances in pathology, genomics, and sequencing methodologies, several commercially available genomic tests have become available that can also help to define the natural history of disease, and in some cases the likelihood of response to specific interventions, such as adjuvant chemotherapy. Although these tests were developed using different methodologies and validated using different patient populations, they have recently been incorporated (to varying degrees) into established breast cancer treatment guidelines, including those of the National Comprehensive Cancer Network (NCCN) and the American Society for Clinical Oncology (ASCO). Despite this, clinicians have unanswered questions on how to use these tests appropriately, the utility of these tests in different patient populations, and how to best incorporate these tests into daily use. In addition, clinicians frequently face challenges when deciding which test is most appropriate to use, and whether one test has any advantages over another.

About the Breast Cancer Therapy Expert Group

The Breast Cancer Therapy Expert Group (BCTEG) is a group of expert physicians and clinical researchers who have dedicated their careers to the treatment of patients with breast cancer. The purpose of the group is to meet periodically to discuss important developments related to breast cancer management, with a particular emphasis on new findings and/or areas where guidance from established bodies, such as NCCN and ASCO, may be unresolved or less well established. The goal is to elicit the group's collective opinions on a given topic as it relates to their own clinical practices, and more importantly, how this might affect oncologists in the community setting, who may not be as extensively versed in breast cancer treatment. Importantly, this article is not intended to replace any existing guidance or guidelines; nor is it an exhaustive review of the topics in question. Rather, it is intended to present a concise synopsis of the relevant data in the area and to summarize the opinion of the expert group as gleaned from the meeting discussion.

Meeting Objectives and Role of Funding Sources

In previous meetings, the group has addressed issues related to ET in early-stage breast cancer, the use of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in patients with metastatic breast cancer, and the treatment of HER2$^-$ positive breast cancer.[1-3] In January 2019, the group convened to discuss issues surrounding the use of genomic testing as a means to guide treatment decisions in EBC. An unrestricted educational grant for this activity was provided by Agendia Inc, BioTheranostics Inc, Myriad Inc, and Nanostring Inc. The faculty members of the BCTEG were selected by Total Health Information Services, a medical information company, based on their expert experience on this topic; they were compensated for their participation. The faculty and Total Health Information Services jointly selected the main topics and general outline for the discussion. It is recognized that many of the panelists may have relationships with corporate entities, both related and unrelated to the topic in question; content of the discussions, and any expert opinions presented herein, is intended to be based on the panelists' own expert clinical experience and insight, and, taking into account current clinical practice guidelines and evidence supporting them, is understood not to be influenced by any corporate relationship or interest.

Genomic Tests

We describe some of the commercially available genomic assays approved for use in breast cancer. Other assays are available, but the assays listed in Table 1 were considered in the discussion because they are the most commonly and currently used and are described in the ASCO and NCCN guidelines.[4-6] The panel also notes that at many institutions there is a "preferred" test, and, because many tests provide similar types of information, often key opinion leaders in breast oncology encourage clinicians to order the test that they are most accustomed to using. In terms of how to decide among tests, the panel thought it was essential for the clinician to first understand the type of information that is provided (or not provided) with each specific test. Whereas some tests provide information that is *prognostic*—that is, providing information about the natural history of disease (eg, risk of recurrence within 5 years), other tests provide information that is *predictive*—that is, providing information on the likely outcome for a specific treatment or intervention (eg, chemotherapy or extended adjuvant [EA] ET). It is also important to recognize that certain biomarkers (eg, ER) are both prognostic (for better outcomes) as well as predictive (for ET benefit). Another notable example in this regard is HER2. Notably, all of these tests can provide prognostic information on recurrence risk for years 0 to 10; 3 of the 5 tests also provide prognostic information more specifically for late recurrence—that is, years 5 to 10. Some tests are also distinguished by their ability to provide predictive information on either chemotherapy benefit (Oncotype DX) or EA ET benefit (Breast Cancer Index) (Table 1). In terms of biopsy starting material needed for genomic testing, the group recognizes that in the past, there had been some differences in the type of tissue needed for the different assays (eg, MammaPrint vs. Oncotype DX). Because all assays now utilize reverse transcription−polymerase chain reaction methodologies, however, formalin-fixed, paraffin-embedded samples can now be used for all assays considered in this review.

Oncotype DX (21-Gene Assay)

This test consists of 16 breast cancer−related genes (including those involved in estrogen signaling and proliferation) as well as 5 reference genes. The assay reports a recurrence score (RS), which ranges from 0 to 100 and initially placed patients into 1 of 3 groups: low risk (RS = 0-17), intermediate risk (RS = 18-30), or high risk (RS = 31-100). The resultant score is both *prognostic* for distant recurrence at 10 years and *predictive* for chemotherapy benefit.[8,9] The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial was the first validation study for the prognostic component of the assay, and patients in the high-risk group (RS $\geq$ 31) had a 30.5% rate of distant recurrence at 10 years, compared to 6.8% for those with RS $<$ 18 (low-risk group; $P < .001$).[8] NSABP B-20 was the first validation study for the predictive component of the assay; those with RS $\geq$ 31 had a 28% absolute benefit from adding chemotherapy to tamoxifen ($P < .001$), whereas those with

Table 1 Commercially Available Genomic Tests in Breast Cancer and Current Guidance

Test	Type of Information Provided	Indication and Current Guidance	Key Prospective Trials (If Available)
Oncotype DX (21-gene assay)	• Prognostic—10-year recurrence risk.	• ASCO: $ER^+/PgR^+/HER2^-$ node-negative disease to guide decisions on systemic adjuvant chemotherapy.[a]	TAILORx
	• Predictive—Adjuvant chemotherapy benefit.	• NCCN: Best validated for its value as a prognostic test and in predicting disease most likely to respond to systemic chemotherapy.[a]	
MammaPrint (70-gene assay)	• Prognostic—10-year recurrence risk.	• ASCO: $ER^+/PgR^+/HER2^-$ node-negative disease and HIGH clinical risk (as per MINDACT criteria)[a] OR $ER^+/PgR^+/HER2^-$ node-positive disease 1-3 positive nodes and HIGH clinical risk (as per MINDACT criteria) to guide decisions on withholding systemic adjuvant chemotherapy.[b]	MINDACT
		• NCCN: No recommendation.	
Breast Cancer Index (BCI)	• Prognostic—10-year recurrence risk; late recurrence risk (5-10 years).	• ASCO: $ER^+/PgR^+/HER2^-$ node-negative disease to guide decisions on systemic adjuvant therapy.[b]	NA
	• Predictive—Extended adjuvant endocrine therapy benefit.	• NCCN: No recommendation.	
EndoPredict (12-gene assay)	• Prognostic—10-year recurrence risk.	• ASCO: $ER^+/PgR^+/HER2^-$ node-negative disease to guide decisions on systemic adjuvant chemotherapy.[b]	NA
		• NCCN: No recommendation.	
Prosigna (50-gene assay)	• Prognostic—10-year recurrence risk.	• ASCO: $ER^+/PgR^+/HER2^-$ node-negative disease to guide decisions on systemic adjuvant therapy in conjunction with other clinicopathologic variables[a]	NA
		• NCCN: No recommendation.	

Unless otherwise specified, tests are not for use in node-positive, $HER2^+$, or triple-negative breast cancers.[4-7]
Abbreviations: ASCO = American Society of Clinical Oncology; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; NA = not applicable; NCCN = National Comprehensive Cancer Network; PgR = progesterone receptor.
[a]Currently strong recommendation.
[b]Currently moderate recommendation.

a low and intermediate (defined as RS between 18 and 30) RS did not gain benefit from chemotherapy.[9] The test was thus the first to distinguish which node-negative, ER^+ patients would benefit from chemotherapy based on the biology of their tumor (RS $\geq$ 31) versus those who were unlikely to derive benefit from chemotherapy (RS $<$ 18).

There remained a question, however, regarding chemotherapy benefit in intermediate-risk patients (RS 18 to 30), which led to the design of the TAILORx trial.[10] In this trial, the intermediate range was shifted to RS 11 to 25 in in order to minimize the potential for undertreatment of patients, as the upper confidence limit for RS 11 represented an approximately 10% recurrence risk, which could be considered a threshold for recommending chemotherapy. TAILORx assigned patients to treatment based on RS, with RS 0 to 10 assigned ET alone, intermediate-risk patients (RS 11 to 25) randomized to chemotherapy or no chemotherapy (all received ET), and those with RS 26 to 100 assigned ET + chemotherapy. Further results from this prospective study are detailed below.

MammaPrint (70-Gene Assay)

This assay was developed from an analysis of untreated breast cancer patients with 20-year follow-up in which 2 risk groups were compared: a low-risk group (with no distant recurrence within 5 years) and a high-risk group (with development of distant metastasis within 5 years). From these studies, a 70-gene assay was developed that was prognostic for early recurrence. Of note, ER, PgR, HER2, and the proliferation marker Ki-67 were not among the 70 genes included in this assay.[11] A validation study was conducted in a European cohort of patients (n = 307) diagnosed between 1980 and 1998 from the TRANSBIG consortium with a median follow-up of 13.6 years; results showed that the 70-gene signature was a strong prognostic indicator for both time to distant metastasis and overall survival (hazard ratio = 2.32 and 2.79, respectively).[12] The results of the MINDACT trial provided the current evidence for the use of MammaPrint in both node-negative (N0) and node-positive (N+) EBC.[13]

Breast Cancer Index

The Breast Cancer Index (BCI) integrates a prognostic 5-gene molecular grade index and a 2-gene predictive biomarker consisting of a ratio of HoxB13 and interleukin-17B receptor (H/I). The test was initially developed as a 2-gene expression biomarker (H/I) capable of identifying a subset of ER^+ patients at risk for recurrence in the setting of tamoxifen therapy; the molecular grade index component of the test was subsequently shown to provide additional prognostic information.[14,15] The prognostic component of the test has been validated in approximately 1300 ER^+/LN^+ patients treated with either tamoxifen or an aromatase inhibitor (AI) across 3 study cohorts.[16,17] The BCI score classifies patients as either low (score 0-5) or high (score 5.1-10) risk for late recurrence in years 5 through 10. In the TransATAC study, those classified as low risk by BCI had a 3.5% rate of late distant recurrence in years 5 to 10.[17] Additional data supporting the potential use of the H/I component of BCI as a predictive biomarker for EA ET benefit are described below.[18]

EndoPredict

This test offers prognostic information on 10-year risk for recurrence for patients with $ER^+/HER2^-$ EBC. It is a 12-gene

molecular score that combines established prognostic factors such as tumor size (T) and node status (N) to generate an individualized score (EPclin) with a binary (low or high risk) result. The test can be used for patients with either node-negative (N0) or node-positive (N+) disease. The test was developed and validated in a population of 964 patients with $ER^+/HER2^-$ disease who had received 5 years of tamoxifen therapy, and was subsequently validated in the ABCSG-6, ABCSG-8, and ATAC cohorts; notably, these populations had not received chemotherapy, received ET only, and included both N0 and N+ patients.[19,20] Data presented at the 2018 San Antonio Breast Cancer Symposium (SABCS) showed that among either N0 or N+ patients, EPclin is prognostic for both early (years 0-10) and late (years 5-15) distant recurrence. In view of the latter result, the test may be useful to determine which patients may be less likely to obtain benefit from EA ET.[21]

Prosigna (PAM50; 50-Gene Assay)

This test, also termed the PAM50 gene expression signature, consists of 50 classifier genes and 5 control genes and is used to define tumors into 1 of the 4 intrinsic subtypes of breast cancer: luminal A, luminal B, $HER2^-$ enriched, and basal-like. In addition, the test provides quantitative data on proliferation, luminal gene expression, *ESR1*, *PGR*, and *ERBB2*.[22,23] The test also allows for the generation of a risk of recurrence score for postmenopausal women with ER^+ breast cancer. The test has been validated for prediction of 10-year recurrence risk in the ATAC trial (postmenopausal women treated with tamoxifen or AI), and in a combined analysis of ATAC and ABCSG-8, the risk of recurrence was predictive for late recurrence (> 5 years) for patients with hormone receptor−positive N0 disease.[24-26] Additional data are available from a Danish cohort of patients, in whom the risk of recurrence score could identify up to 37% of LN^+ patients who could be spared chemotherapy with good outcomes (< 5% distant recurrence at 5 years).[27]

Available Prospective Data: MINDACT and TAILORx

MINDACT and TAILORx are two important trials that have prospectively examined the value of genomic testing in EBC patients, and results from these trials have helped to shape the current ASCO and NCCN guidance in this area.[4-6] These trials are summarized in Table 2. In TAILORx, the 21-gene score (Oncotype DX) was used to define a population of patients (n = 6,711, ~ 69% of the total population) with an intermediate RS of 11 to 25, in whom the benefit of chemotherapy had previously been unclear.[10] The overall results of the trial showed that adjuvant ET alone and chemo-ET were equally efficacious in this group of patients, with similar rates of invasive disease-free survival (DFS), freedom from distant recurrence, and overall survival. Some benefit of chemotherapy, however, was found in an exploratory analysis examining the benefit of chemotherapy according to age. For example, for patients < 50 years of age, the addition of chemotherapy improved invasive DFS by 2.7% in the RS 16 to 20 group, and by 5.8% in the RS 21 to 25 group. The group noted that this latter finding could be related to the off-target effects of chemotherapy resulting in premature menopause, a notable adverse effect associated with improved DFS.[10] The group also acknowledges that findings in the under-50 age group have unfortunately added to the complexity of interpreting results of the Oncotype DX report. Overall, however, the TAILORx trial provides level 1 data that a sizable proportion of EBC patients can be identified using the 21-gene assay who can be spared adjuvant chemotherapy. A paper published after our consensus conference further subdivided the TAILORx population based on clinical risk (as defined by a modification of Adjuvant! Online). The only substantive addition from this paper was to define clinically low-risk patients with scores of 16 to 20 as not benefiting from chemotherapy, while clinically high-risk patients with RS 16 to 20 had benefit similar to those with RS 21 to 25.[28]

It is important to note that the majority of patients (74%) randomized in TAILORx were clinically low risk, and that even patients who were clinically high risk (26%) and who had a low RS, a benefit to chemotherapy could not be identified.[10] Notwithstanding the results of TAILORx, some panelists noted that there remains a gray zone for women with an RS of 26 to 30, as it is still unclear exactly where the benefit of chemotherapy begins, and currently no prospective randomized data exist for these patients. Current standard of care, however, dictates that chemotherapy should be offered to these patients. Another noted caveat of the TAILORx trial was that ovarian suppression was only received by approximately 13% of patients, with 87% of the patients receiving only tamoxifen monotherapy; in this regard, the panelists thought that the benefit of chemotherapy in the under-50 group may be related to the effects of chemotherapy on ovarian suppression. Indeed, such an effect has been demonstrated to be of importance in the longer follow-up of the SOFT/TEXT trials.[29] While not recommending any one test over another, NCCN guidelines currently recognize the 21-gene test as best validated/preferred assay in hormone receptor−positive/$HER2^-$/N0 patients to predict the benefit of chemotherapy (Table 1).

Additional data are expected from the RxPONDER trial regarding the use of this test in node-positive patients (NCT01272037); some in the group thought that the number of patients and events is too limited to make a clear recommendation at this time for patients with LN^+ disease and that results from RxPONDER should be awaited. The NCCN panel, however, has noted results from a secondary analysis of the retrospective subset analysis of the prospective SWOG 8814 study. This analysis showed, for patients with 1 to 3 positive LNs, no benefit of chemotherapy in those with low RS, whereas a benefit was shown for those with high RS $\geq$ 31; it also noted that the optimal cutoff to withhold chemotherapy is unknown for patients with RS 11 to 25 at present.[6,30] Some panelists also noted the results from West German Study Group (WSG) PlanB, a prospective trial that showed excellent 3- and 5-year DFS (98% and 94%, respectively) for patients with high clinical risk (~ 62% grade 2; ~ 35% N1) and RS $\leq$ 11.[31,32] Important to note, however, are the limitations of the WSG trial, in that the clinical consequence of omitting chemotherapy could only be assessed for the small group of patients with RS < 11; indeed, a majority of patients (~ 60%) had RS 12 to 25, and the clinical benefit of chemotherapy in this group is at present unclear.[31]

In MINDACT, the 70-gene signature (MammaPrint) was used to identify a population of clinically (as defined using a modified version of Adjuvant! Online) and genomically (as defined by MammaPrint) discordant patients who were then randomized to

Table 2 Summary of Available Prospective Data in Genomic Testing for TAILORx and MINDACT Trials[10,13]

Trial	Population Studied	Main Objective	Key Findings	Implications for Practice
TAILORx	• N = 10,273 women (18-75 years) with hormone receptor − positive/HER2$^-$/axillary N0 breast cancer meeting NCCN criteria for consideration of CT.	To determine whether, among patients with an intermediate score by 21-gene assay (Oncotype DX), ET alone is noninferior to ET + CT.	• ET was noninferior to ET + CT for invasive disease-free survival at 9 years (83.3% vs. 84.3%; HR = 1.08; 95% CI = 0.94-1.24; P = .26).	• Adjuvant CT was not beneficial for patients with an intermediate RS of 11-25 on the 21-gene assay (Oncotype DX).
	• N = 6711 with intermediate RS 11-25.		• Similar results seen for freedom from disease recurrence at a distant site (94.5% and 95.0%) and overall survival (93.9% and 93.8%).	• Use of the assay could identify up to 85% of early breast cancer patients who can be safely spared CT (RS = 25 or less).
			• Varying degrees of CT benefit demonstrated in women ≤ 50 years with RS of 16 to 25.	• For patients < 50, consideration should be given to offering CT.
MINDACT	• N = 6693 women (18-70 years) with primary invasive early breast cancer (stage T1/T2/operable T3); 79% had N0 disease.	To determine whether women with high risk clinical (C) features and low genomic (G) risk (C-high/G-low) who did not receive CT had noninferior outcomes to those who did receive CT.	• Total of 1550 patients (23.2%) had C-high/G-low status; 5-year DMFS was 94.7% among patients in this group who did not receive CT, meeting the criteria for noninferiority.	• The 70-gene signature (MammaPrint) can be useful to identify a subset of high-clinical-risk patients with a low genomic risk (C-high/G-low) who can safely forgo CT without impairing outcomes.
	• Clinical and genomic risk determined by modified Adjuvant! Online and 70-gene assay (MammaPrint).		• Prespecified secondary analysis showed that for patients with C-high/G-low status, the rate of distant metastasis-free survival was 1.5 percentage points lower than those who did receive CT (95.9% vs. 94.4%). The result was not statistically significant. The findings were consistent in node-positive and node-negative patients. Trial was not sufficiently powered to identify a benefit to CT in this group.	• The findings represent the only prospective data set supporting a decision to safely forgo CT in a node-positive population.
				• For C-low/G-high, patients, a benefit to CT could not be demonstrated.
				• Long-term results are pending; 10-year follow-up analysis planned.

Abbreviations: CI = confidence interval; CT = chemotherapy; DMFS = distant metastasis-free survival; ER = estrogen receptor; ET = endocrine therapy; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; NCCN = National Comprehensive Cancer Network; RS = recurrence score.

receive or not receive adjuvant chemotherapy based on their clinical risk or their genomic risk. The subset of clinically high-risk (C-high) patients who were genomically low risk (G-low) included 1550 patients (~ 23% of the total population). Patients with discordant results (ie, either C-high/G-low or C-low/G-high) were randomly assigned to the chemotherapy group or the no-chemotherapy group based on either the clinical result or the genomic result. The objective was to determine whether women with high risk clinical (C) features and low genomic (G) risk (C-high/G-low) who did not receive chemotherapy had noninferior outcomes to those who did receive chemotherapy. The primary objective of the study was to show whether the lower boundary of the 95% confidence interval for the rate of survival without distant metastasis would be at least 92%, and this primary endpoint was met, given that patients who were C-high and G-low who did not receive adjuvant chemotherapy (primary-test population) had a rate of survival without distant metastasis of 94.7% (95% confidence interval, 92.5-96.2). In secondary analyses for chemotherapy benefit (not adequately powered to detect small differences), the 5-year rate of survival without distant metastasis was 1.5 percentage points higher for patients in the C-high/G-low group who received adjuvant chemotherapy versus those who did not (a finding that was not statistically significant).[13] The results thus imply that a sizable proportion of patients can be identified using MammaPrint who have good outcomes and can safely forgo chemotherapy.

Results for the C-low/G-high group, by comparison, showed that there was no difference in 5-year distant metastasis-free survival when assigning treatment based on clinical risk (ie, no chemotherapy, 95.0%) or when assigning treatment based on genomic risk (ie, with chemotherapy, 95.8%). The results thus imply no advantage of assigning treatment based on genomic risk in clinically low-risk patients. Despite the findings of MINDACT, however, it was acknowledged that longer follow-up is needed, and a 10-year follow-up is planned. In this regard, some panelists noted results from the Early Breast Cancer Trialist's Collaborative Group (EBCTCG) on 20-year recurrence risk, showing that most of the chemotherapy benefit occurs early in the course of disease.[33] Therefore, the 5-year follow-up in MINDACT was likely sufficient to identify a potential chemotherapy benefit. It should also be noted that the Adjuvant! Online feature is currently off-line and not available. In this regard, some in the group thought that the recent 2019 publication by Sparano et al[12] might be helpful to define cutoff points for clinical risk, referring to the so-called rule of 4 (> 3 cm + grade 1; > 2 cm + grade 2; > 1 cm + grade 3).

Comparative Retrospective Data

The remaining tests—BCI, Prosigna, and EndoPredict—have thus far not been evaluated prospectively, and data supporting their use as a means to guide treatment decisions are limited to retrospective evaluations across different clinical trial populations. In 2018, Sestak et al[34] published a comparison of 6 prognostic tests across the same patient population (n = 774 postmenopausal women with $ER^{+}/HER2^{-}$ breast cancer) with long-term follow-up data. This comparison included 2 prognostic algorithms, clinical treatment score (CTS) and the 4-marker immunohistochemical score (IHC4), and 4 gene expression signatures (Oncotype DX, BCI, PAM50, and EPclin); notably, all 6 of these tests had been previously evaluated in the same cohort of patients from the TransATAC study.[17,20,24,34,35] The results showed that all of the signatures provided prognostic information during years 0 to 10 from women with N0 disease (n = 591), whereas the prognostic strength was weaker for the smaller number of N+ patients with 1 to 3 positive nodes (n = 183).[34]

With respect to late distant recurrence, however, BCI, PAM50, and EPclin provided independent prognostic information for both N0 patients and those with 1 to 3 positive nodes; the authors speculated that there may be components of these signatures that are more prognostic for recurrence in years 5 to 10, and as such could be used to provide information on the need for EA ET to reduce recurrence risk. The study also showed that the combination of molecular features with clinical factors (eg, EPclin) was more informative, particularly for patients with N+ disease.[34] Likelihood ratios were used to compare the prognostic information provided by each test relative to the CTS; in each case, these comparisons favored BCI, PAM50, and particularly EPclin, all of which provided significant independent prognostic information above the CTS for late recurrence. Some in the group thought it was important to caution that the likelihood ratios provided simply represent statistical comparisons among the tests, and therefore do not provide clinical utility favoring any one test over another.

The panelists also noted the data supporting the use of BCI as a predictive biomarker for EA ET benefit. The predictive ability of this biomarker was demonstrated in the MA.17 trial, which evaluated the use of letrozole, an AI, in the EA setting. Specifically, for those with a high H/I ratio, there was a significant reduction in recurrence with EA letrozole, from 27.0% to 10.7% ($P = .007$), whereas for those with a low H/I ratio, there was no statistically significant reduction in recurrence with EA letrozole therapy ($P = .35$).[18] In view of the limited absolute DFS benefit of EA therapy with AIs (2-4.7%) and the risk for toxicity (eg, myalgias, osteoporosis, and/or fracture), this test may be useful to distinguish patients who are most likely to benefit from EA treatment with letrozole (or another AI) versus those who will not benefit (and consequently could be safely spared EA ET).[36-38] In a further analysis of N1 patients (1-3 positive nodes), a BCI model incorporating tumor size and grade could identify 20% of N1 patients with a low risk of distant recurrence over 15 years (1.3%) who might be safely spared EA ET.[39] Despite these data, however, the panel notes that current ASCO and NCCN guidelines, while supporting use of BCI as a prognostic indicator, do not support its use as a predictive marker for EA ET benefit.[5-7] Although not discussed at the meeting, the group also acknowledges that tools such as the Clinical Treatment Score Post−5 Years (CTS5) are available to help inform EA therapy decisions; recent findings have validated this clinicopathologic tool for predicting late recurrence in a large unselected patient population.[40]

Genomic Testing: Practical Considerations

Some general clinical practice points on genomic testing in breast cancer are summarized in Table 3. The panel suggested that the clinician should have 3 main considerations when deciding on genomic testing: first, whether is there a need for genomic testing at

Table 3 Genomic Testing in Breast Cancer: Clinical Practice Points

• Genomic testing is generally only indicated in patients with hormone receptor–positive (ER^+/PgR^+) and $HER2^-$ tumors, and those with up to 3 positive nodes.
• Genomic testing should generally not be performed for patients with hormone receptor–negative disease, > 3 positive nodes, HER2 positivity, or TNBC outside the context of a clinical trial.
• Genomic testing should generally not be performed in patients for whom the results of the testing will not affect the course of treatment.
• Importantly, neither ASCO nor NCCN guidelines currently imply the superiority of any one genomic test over another.
• Discordance between available genomic tests is expected because the different tests were developed and validated across a range of patient populations and treatment backgrounds; performing more than one genomic test on a patient should be avoided, as uncertainties in risk assignment may result.

Abbreviations: ASCO = American Society of Clinical Oncology; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; NCCN = National Comprehensive Cancer Network; PgR = progesterone receptor; TNBC = triple-negative breast cancer.

all; second, which of the available tests should be ordered; and third, how the results of the test should be interpreted. In this regard, the panel suggested that at present, genomic testing should be limited to patients with ER^+, $HER2^-$ EBC, whereas the benefit of testing has been less widely investigated in other patient groups, including those with triple-negative tumors, $HER2^+$ disease, and those with 4 or more positive LNs. Another essential concept is to recognize that because the currently available tests were developed and validated across different patient populations and treatment backgrounds, they should not be considered interchangeable, and discordance between the genomic tests is to be expected (eg, a patient having a high risk score on one test vs. low or intermediate score on another). To avoid this situation, which can introduce further uncertainties and ambiguities regarding treatment, it is strongly recommended that only one test be performed for each patient sample.

Another general point emphasized was that genomic testing should not be ordered if the outcome of the test will not change the course of treatment—for example, if the patient would not consider chemotherapy under any circumstance, has commodities that render the patient inappropriate for chemotherapy, or has clinicopathologic features that are clearly more informative. In other cases, such as N+ disease (1-3 positive nodes, where genomic testing has been generally less well validated), it was thought that results of genomic testing could be useful in the process of shared clinical decision making; if considering chemotherapy, for example, the results would be considered along with whether the patient is a valid candidate for chemotherapy, and the patient's overall willingness to undergo chemotherapy. It was also recognized by the group that there are a number of alternative scoring systems available that are intended to either replace or supplement the use of molecular assays; these include algorithms such as the CTS, 4-marker immunohistochemical score (IHC4), and the McGee equation, which are not included in the current ASCO or NCCN guidelines. Some of these alternatives have shown a high rate of concordance with other commercially available assays in assigning risk.[41] Some in the group also noted, however, that although useful, alternative assays such as the McGee equation and IHC4 are not recommended because they are simply looking at rate of concordance with other genomic tests, and they have also only been tested in small numbers of patients with few data on long-term outcomes.

Clinical Scenarios

We present below several breast cancer clinical scenarios that might be encountered in which the need for molecular testing might be considered. In each scenario, the group aims to answer the questions of whether genomic testing would be appropriate for the patient and which test might be most appropriately used, based on the available data and clinical guidance that were in place at the time of the January 2019 meeting. It is recognized that more than one test might be applicable for each case, but preference was given to those assays with prospective supporting data. The group also recognizes that other factors such as patient preference, cost, accessibility, and coverage issues might also affect the decision on whether to test and which assay to use, and it was not the intent of the group to endorse any one test over another. For cases where adjuvant chemotherapy decisions apply, MammaPrint, Oncotype DX, EndoPredict, and PAM50 were considered. Although the NCCN and ASCO recognize the BCI as a diagnostic assay having the ability to prognosticate patients who have good outcomes without chemotherapy,[4,5] most in the group thought that the BCI would not be used in ordinary clinical practice to guide chemotherapy decisions. Therefore, BCI was not considered in these case scenarios. Instead, most panelists believed that BCI should be ordered in situations where there was uncertainty about the use of EA ET. It was also noted that, if considering ordering BCI, it might first be determined whether the patient will actually be compliant with the ET; for example if a patient was known to be noncompliant with the ET in question, then ordering the test would be less useful.

Set 1: Chemotherapy Decisions: The Clinical "High-Risk" Patient

1A The first case scenario considered a younger patient (40 years old) with N+ disease; the patient's tumor is grade 2 (T2/N1), ER^+, and $HER2^-$.

Test	Applicability	Type of Evidence	Relevant Prospective Randomized Study
MammaPrint	Most applicable	Prospective	MINDACT
Oncotype DX	Applicable	Prospective	WSG PlanB
Prosigna PAM50	Applicable	Retrospective	NA
EndoPredict	Applicable	Retrospective	NA

Discussion. For this patient, the key question that genomic testing could help inform is whether the patient should receive adjuvant chemotherapy. In this example, the group noted that MammaPrint

would be most appropriately used, as this test can identify a subgroup of patients that would do very well without chemotherapy, based on the prospective data (MINDACT). Although other tests may be applicable in this case, their use would be justified based on limited prospective and retrospective data. Importantly, the ASCO guidance is specific to MammaPrint for patients with 1 to 3 positive nodes. Panelists also note here the results from the WSG PlanB trial, which show excellent outcomes for patients with high-risk clinical features who have RS < 11 using Oncotype DX. However, if a more intermediate RS (eg, scores of 16-20, 21-25) was obtained, this could lead to some confusion based on the results of TAILORx in the under-50 age group.[31,32] In addition, the small number of patients with N+ disease studied in both MINDACT and WSG PlanB must be borne in mind, and as such, it would be equally reasonable for the clinician to forego genomic testing in this patient and proceed with chemotherapy until further prospective data are available.

1B For the second case, the group considered an older patient (65 years old) having no comorbid conditions, with node-negative disease. The patient's tumor is 1.9 cm and grade 3, ER$^+$, HER2$^-$, and N0.

Test	Applicability	Type of Evidence	Relevant Prospective Randomized Study
Oncotype DX	Most applicable	Prospective	TAILORx
MammaPrint	Applicable	Prospective	MINDACT
Prosigna PAM50	Applicable	Retrospective	NA
EndoPredict	Applicable	Retrospective	NA

Discussion. For this clinically high-risk patient, the key question is again which genomic test could help decide whether the patient should receive adjuvant chemotherapy. Although the group considers that prospective data are available for both MammaPrint and Oncotype DX in this scenario, it should be noted that MammaPrint provides only prognostic not predictive data (for chemotherapy benefit) in this case.

Set 2: Chemotherapy Decisions: The Clinical "Low-Risk" Patient

2A The group then considered patients in the clinical low-risk category, specifically a 65-year-old postmenopausal woman with a pT1c (1.0 cm), N0, grade 1, ER$^+$ (99%), PgR$^+$ (95%), HER2$^-$, invasive ductal carcinoma.

Test	Applicability	Type of Evidence	Relevant Prospective Randomized Study
Oncotype DX	Applicable	Prospective	TAILORx
MammaPrint	Less applicable	Prospective	MINDACT
Prosigna PAM50	Less applicable	Retrospective	NA
EndoPredict	Less applicable	Retrospective	NA

Discussion. The group thought that genomic profiling in general may be less applicable for this patient, given the small tumor size, low grade, and high hormone receptor positivity. In fact, it was noted by some panelists that such a patient would not be tested in Europe but would instead be treated with ET alone, as the chance for a clinically low-risk patient having a high genomic risk is low, and genomic testing is not considered cost-effective in this setting. Oncotype DX would be applicable for this patient, based on prospective findings from TAILORx, which included such patients. MammaPrint is not applicable for clinical low-risk patients because even with a high MammaPrint result (C-low/G-high), there was no chemotherapy benefit shown in MINDACT. Prosigna PAM50 and EndoPredict are also useful for long-term prognostication of this patient, but their applicability would be based on retrospective data.[19,34]

2B A second example considered by the group in the low-risk category was an elderly patient (78 years old) with an 8 mm, grade 1 tumor that is ER$^+$, HER2$^-$, and N0.

Discussion. In this scenario, it was agreed that based on the patient's age and tumor size, genomic testing would not be useful. Although some guidance (eg, NCCN) would recommend testing based on tumor size alone (> 5 mm), other international guidance (eg, St. Gallen) suggest that testing would not be cost-effective in this low-risk patient.

Set 3: Endocrine Therapy Decisions

3A For this scenario, the group considered a postmenopausal woman (48 years old) who was perimenopausal at the time of diagnosis; her tumor was 2 cm and grade 3 with 1 positive node. She subsequently received adjuvant chemotherapy and has just completed 5 years of adjuvant tamoxifen.

Test	Applicability	Type of Evidence	Relevant Prospective Randomized Study
BCI	Most applicable	Retrospective	NA
MammaPrint	Applicable	Retrospective	MINDACT
Oncotype DX	Applicable	Retrospective	TAILORx
Prosigna PAM50	Applicable	Retrospective	NA
EndoPredict	Applicable	Retrospective	NA

Discussion. In this scenario, genomic testing could be useful to determine whether this high-risk patient should receive an additional 5 years of adjuvant ET with a switch to an AI. BCI was considered most appropriately used in this scenario because it provides both prognostic information on late recurrence risk (in this case, after 5 years of adjuvant tamoxifen) as well as predictive information of EA ET benefit. Whereas the remaining tests can provide useful prognostic information on late recurrence, they are not currently utilized to determine the benefit of EA ET. Some panelists also noted a secondary analysis of the MA.17 trial, which demonstrated that premenopausal women (at the time of diagnosis) who became menopausal experienced a greater than 70% reduction

Table 4 Genomic Testing in HR$^+$/HER2$^-$ Node-Positive Breast Cancer in RxPONDER and OPTIMA Trials

Study	Study Population	Study Description and Primary Endpoint	Timeline
RxPONDER [NCTNCT01272037]	• HR$^+$/HER2$^-$ disease.	• Phase 3 study of standard adjuvant ET (tamoxifen or AIs) with or without chemotherapy.	Forthcoming; primary completion estimated for 2022.
	• 1 to 3 positive nodes.	• Cox regression will be used to examine the interaction of linear RS with chemotherapy benefit; goal will be to define a cut point for recommending chemotherapy for patients with RS 0 to 25.	
	• Oncotype DX (21-gene assay) RS of 25 or less.		
OPTIMA [research.uk]	• HR$^+$/HER2$^-$ disease.	• Phase 3 study examining the impact of chemotherapy with 5 to 10 years' ET in patients with HR$^+$/HER2$^-$ node-positive disease.	Forthcoming; trial is currently recruiting until 2021.
	• Age $\geq$ 40 years.	• Group 1 will receive chemo-ET without testing	
	• Chemotherapy eligible.	• In group 2, Prosigna (50-gene assay) will be used to stratify patients to chemo-ET or ET alone.	
	• Up to 9 LNs positive[a]; or LN0 with $\geq$ 30 mm tumor.		

Abbreviations: AI = aromatase inhibitor; ET = endocrine therapy; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; LN = lymph node; RS = recurrence score.
[a]If only 1 to 3 nodes positive, spread across > 2 mm across in at least 1 node; or if tumor > 20 mm spread to 1 to 3 nodes and < 2 mm across in each node.

in recurrence with the addition of letrozole; the role of BCI in this subgroup of patients remains unclear.

3B Decisions regarding EA ET may also apply to low-risk patients; for this example, the group considers a 64-year-old patient with a grade 2 tumor that is node negative (T2/N0) ER$^+$ (80%), PgR$^+$ (70%), and HER2$^-$. The patient received adjuvant tamoxifen for 5 years but is concerned about extending adjuvant therapy with an AI for fear of adverse events and concern about having a late recurrence.

Test	Applicability	Type of Evidence	Relevant Prospective Randomized Study
BCI	Most applicable	Retrospective	MA.17
MammaPrint	Applicable	Retrospective	NA
Oncotype DX	Applicable	Retrospective	NA
Prosigna PAM50	Applicable	Retrospective	NA
EndoPredict	Applicable	Retrospective	NA

Discussion. For this patient, the concern once again is whether to extend ET for this lower-risk patient, and it would be desirable to determine the patient's late recurrence risk (years 5-10) as well as her likelihood of response to ET. Whereas all of the assays can provide information on years 0 to 10 recurrence risk, based on retrospective analyses, BCI, PAM50, and EPclin are more prognostic for late recurrence (years 5-10).[34] Because BCI is also predictive for EA ET benefit in the MA.17 trial, it is most applicable in this case.[17]

Conclusions

Genomic assays in breast cancer provide an additional tool for the clinician to help refine treatment decisions, including the use of adjuvant chemotherapy or EA ET; these tests should be used to assist in shared decision making between the patient and oncologist. When deciding whether to test a patient, clinicians should consider the overall need for the test, which test is most appropriate, and how the expected results of the testing should be interpreted. It is also important for oncologists to understand and differentiate among the available genomic tests by the type of information provided (prognostic or predictive), bearing in mind that some tests provide both types of information. Some panelists also thought that the most useful tests are those that provide both prognostic information (eg, 10-year recurrence risk) as well as predictive information (eg, the benefit of chemotherapy). Other panelists, however, thought that even determination of overall prognosis alone was useful for them when making treatment decisions.

The panelists cited several examples of patients for whom genomic testing would not be indicated—for example, an older patient with a grade 1 subcentimeter tumor, or a patient with 3 or more positive nodes. There was general consensus that genomic testing should not be done for patients in whom the outcome will not change the course of treatment—for example, if the clinician already knows the patient is not suitable to receive chemotherapy (eg, due to age, comorbid conditions) or would decline chemotherapy. Although some tests (eg, Oncotype DX, MammaPrint) had been more widely used by the panelists and have the added value of prospective data to support their indications, the panel agreed there is currently insufficient evidence to recommend any one test over another, and ASCO and NCCN guidelines are reflective of this.

Last, although not discussed formally at the meeting, the group notes that overall data on the benefit/clinical utility of genomic testing are at present limited in several settings, such as younger women (< 30 years of age), male breast cancer patients, the neoadjuvant setting, and patients with positive LNs. Forthcoming results from trials such as RxPONDER and OPTIMA should help assess the benefit of genomic testing in relation to receipt or nonreceipt of chemotherapy, particularly for patients with N+ disease (Table 4). In RxPONDER (NCT01272037), patients will have ER$^+$/HER2$^-$ disease with 1 to 3 positive nodes and an RS of 25 or less.[42] In OPTIMA, patients will have ER$^+$/HER2$^-$ disease with 1 to 9 positive nodes, or N0 disease with tumor size

> 30 mm.[43] Additional data are also needed with longer-term outcomes in patients who have high-risk clinical features but whose genomic risk is scored low and who might be spared chemotherapy.

Note Added in Proof

After this meeting, an update to the ASCO 2016 guidance was published that incorporated results from TAILORx (Andre F, et al. *J Oncol Pract* 2019, JOP1900264; Andre F, et al. *J Clin Oncol* 2019; 37: 1956-64). In the setting of patients with $ER^+/HER2^-$/N0 disease, strong recommendations were made to consider ET alone for (1) patients $\geq$ 50 years with RS $<$ 26, and (2) patients $\leq$ 50 years with RS $<$ 16, and also to consider chemo-ET for all patients with RS $>$ 30. Moderate recommendations were made to consider chemo-ET for patients $\leq$ 50 years with RS 16 to 25, and in all those with RS 26 to 30. Further guidance from ASCO regarding use of the 21-gene assay in node-positive disease is also expected soon.

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