ABSTRACT

• **Objectives:** To describe common genomic tests being used clinically to assess prognosis and guide adjuvant chemotherapy and endocrine therapy decisions for early-stage breast cancer.

• **Methods:** Case presentation and review of the literature.

• **Results:** Hormone receptor–positive (HR-positive) breast cancers, which express the estrogen and/or progesterone receptor, account for the majority of breast cancers. Endocrine therapy can be highly effective for patients with these HR-positive tumors, and identification of HR-positive breast cancers that do not require the addition of chemotherapy is critical. Clinico-pathological features of the breast cancer, including tumor size, nodal involvement, grading, and HR status, are insufficient in predicting the risk for recurrence or the need for chemotherapy. Furthermore, a portion of HR-positive breast cancers have an ongoing risk for late recurrence, and longer durations of endocrine therapy are being used to reduce this risk.

• **Conclusion:** There is sufficient evidence for use of genomic testing in early-stage HR-positive breast cancer to aid in chemotherapy recommendations. Further confirmation of genomic assays for prediction of benefit from prolonged endocrine therapy is needed.

Key words: molecular testing; decision aids; HR-positive cancer; recurrence risk; adjuvant chemotherapy; endocrine therapy.

Despite the increase in incidence of breast cancer, breast cancer mortality has decreased over the past several decades. This is likely due to both early detection and advances in systemic therapy. However, with more widespread use of screening mammography, there are increasing concerns regarding potential overdiagnosis of cancer [1]. One key challenge is that breast cancer is a heterogeneous disease. Thus, improved tools for determining breast cancer biology can help physicians individualize treatments, with low-risk cancers approached with less aggressive treatments, thus preventing unnecessary toxicities, and higher-risk cancers treated appropriately.

Traditionally, adjuvant chemotherapy was recommended based on tumor features such as stage (tumor size, regional nodal involvement), grade, expression of hormone receptors (estrogen receptor [ER] and progesterone receptor [PR]) and human epidermal growth factor receptor-2 (HER2), and patient features (age, menopausal status). However, this approach is not accurate enough to guide individualized treatment recommendations, which are based on the risk for recurrence and the reduction in this risk that can be achieved with various systemic treatments. In particular, there are individuals with low-risk HR-positive, HER2-negative breast cancers who could be spared the toxicities of cytotoxic chemotherapies without compromising the prognosis.

Beyond chemotherapy, endocrine therapies also have risks, especially when given for extended durations. Recently, extended endocrine therapy has been shown to prevent late recurrences of HR-positive breast cancers. In the MA.17R study, extended endocrine therapy with letrozole for a total of 10 years (beyond 5 years of an aromatase inhibitor [AI]) decreased the risk for breast cancer recurrence or the occurrence of contralateral breast cancer by 34% [2]. However, the overall survival was similar between the 2 groups and the results were not confirmed in other studies [3–5]. Identifying the subgroup of patients who benefit from this extended AI therapy is important in the era of personalized medicine. Several tumor genomic assays have been developed to

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provide additional prognostic and predictive information with the goal of individualizing adjuvant therapies for breast cancer. Although assays are also being evaluated in HER2-positive and triple negative breast cancer, this review will focus on HR-positive, HER2-negative breast cancer.

**CASE STUDY**

**Initial Presentation**

A 54-year-old postmenopausal woman with no significant past medical history presents with an abnormal screening mammogram, which shows a focal asymmetry in the 10 o’clock position at middle depth of the left breast. Further work-up with a diagnostic mammogram and ultrasound of the left breast shows a suspicious hypoechoic solid mass with irregular margins measuring 17 mm. The patient undergoes an ultrasound-guided core needle biopsy of the suspicious mass, the results of which are consistent with an invasive ductal carcinoma, Nottingham grade 2, ER strongly positive (95%), PR weakly positive (5%), HER2 negative, and Ki-67 of 15%. She undergoes a left partial mastectomy and sentinel lymph node biopsy, with final pathology demonstrating a single focus of invasive ductal carcinoma, measuring 2.2 cm in greatest dimension with no evidence of lymphovascular invasion. Margins are clear and 2 sentinel lymph nodes are negative for metastatic disease (final pathologic stage IIA, pT2 pN0 cM0). She is referred to medical oncology to discuss adjuvant systemic therapy.

- Can additional testing be used to determine prognosis and guide systemic therapy recommendations for early-stage HR-positive/HER2-negative breast cancer?

After a diagnosis of early-stage breast cancer, the key clinical question faced by the patient and medical oncologist is: what is the individual’s risk for a metastatic breast cancer recurrence and thus the risk for death due to breast cancer? Once the risk for recurrence is established, systemic adjuvant chemotherapy, endocrine therapy, and/or HER2-directed therapy are considered based on the receptor status (ER/PR and HER2) to reduce this risk. Hormone receptor (HR)–positive, HER2-negative breast cancer is the most common type of breast cancer. Although adjuvant endocrine therapy has significantly reduced the risk for recurrence and improved survival for HR-positive breast cancer [6], the role of adjuvant chemotherapy for this subset of breast cancer remains unclear. Prior to genomic testing, the recommendation for adjuvant chemotherapy for HR-positive/HER2-negative tumors was primarily based on patient age and tumor stage and grade. However, chemotherapy overtreatment remained a concern given the potential short- and long-term risks of chemotherapy. Further studies into HR-positive/HER2-negative tumors have shown that these tumors can be divided into 2 main subtypes, luminal A and luminal B [7]. These subtypes represent unique biology and differ in terms of prognosis and response to endocrine therapy and chemotherapy. Luminal A tumors are strongly endocrine responsive and have a good prognosis, while luminal B tumors are less endocrine responsive and are associated with a poorer prognosis; the addition of adjuvant chemotherapy is often considered for luminal B tumors [8]. Several tests, including tumor genomic assays, are now available to help with delineating the tumor subtype and aid in decision-making regarding adjuvant chemotherapy for HR-positive/HER2-negative breast cancers.

**Tests for Guiding Adjuvant Chemotherapy Decisions**

**Ki-67 Assays, Including IHC4 and PEPI**

Chronic proliferation is a hallmark of cancer cells [9]. Ki-67, a nuclear nonhistone protein whose expression varies in intensity throughout the cell cycle, has been used as a measurement of tumor cell proliferation [10]. Two large meta-analyses have demonstrated that high Ki-67 expression in breast tumors is independently associated with worse disease-free and overall survival rates [11,12]. Ki-67 expression has also been used to classify HR-positive tumors as luminal A or B. After classifying tumor subtypes based on intrinsic gene expression profiling, Cheang et al determined that a Ki-67 cut point of 13.25% differentiated luminal A and B tumors [13]. However, the ideal cut point for Ki-67 remains unclear, as the sensitivity and specificity in this study was 77% and 78%, respectively. Others have combined Ki-67 with standard ER, PR, and HER2 testing. This IHC4 score, which weighs each of these variables, was validated in postmenopausal patients from the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial who had ER-positive tumors and did not receive chemotherapy [14]. The prognostic information from the IHC4 was
similar to that seen with the 21-gene recurrence score (Oncotype DX), which is discussed later in this article. The key challenge with Ki-67 testing currently is the lack of a validated test methodology, and intraobserver variability in interpreting the Ki-67 results [15]. Recent series have suggested that Ki-67 be considered as a continuous marker rather than a set cut point [16]. These issues continue to impact the clinical utility of Ki-67 for decision making for adjuvant chemotherapy.

Ki-67 and the preoperative endocrine prognostic index (PEPI) score have been explored in the neoadjuvant setting to separate postmenopausal women with endocrine-sensitive versus intrinsically resistant disease and identify patients at risk for recurrent disease [17]. The on-treatment levels of Ki-67 in response to endocrine therapy have been shown to be more prognostic than baseline values, and a decrease in Ki-67 as early as 2 weeks after initiation of neoadjuvant endocrine therapy is associated with endocrine-sensitive tumors and improved outcome. The PEPI score was developed through retrospective analysis of the P024 trial [18] to evaluate the relationship between post-neoadjuvant endocrine therapy tumor characteristics and risk for early relapse. This was subsequently validated in an independent data set from the IMPACT trial [19]. Patients with low pathological stage (0 or 1) and a favorable biomarker profile (PEPI score 0) at surgery had the best prognosis in the absence of chemotherapy. On the other hand, higher pathological stage at surgery and a poor biomarker profile with loss of ER positivity or persistently elevated Ki-67 (PEPI score of 3) identified de novo endocrine-resistant tumors which are at higher risk for early relapse [20]. The ongoing Alliance A011106 ALTERNATE trial (ALTERNATE approaches for clinical stage II or III Estrogen Receptor positive breast cancer NeoAdjuvant TrEatment in postmenopausal women, NCT01953588) is a phase 3 study to prospectively test this hypothesis.

### 21-Gene Recurrence Score (Oncotype DX Assay)

The 21-gene Oncotype DX assay is conducted on paraffin-embedded tumor tissue and measures the expression of 16 cancer-related genes and 5 reference genes using quantitative polymerase chain reaction. The genes included in this assay are mainly related to proliferation (including Ki-67), invasion, and HER2 or estrogen signaling [21]. Originally, the 21-gene recurrence score assay was analyzed as a prognostic biomarker tool in a prospective-retrospective biomarker substudy of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 clinical trial in which patients with node-negative, ER-positive tumors were randomly assigned to receive tamoxifen or placebo without chemotherapy [22]. Using the standard reported values of low risk (< 18), intermediate risk (18–30), or high risk (≥ 31) for recurrence, among the tamoxifen-treated patients, cancers with a high-risk recurrence score had a significantly worse rate of distant recurrence and overall survival [21]. Inferior breast cancer survival with a high recurrence score was also confirmed in other series of endocrine-treated patients with node-negative and node-positive disease [23–25].

The predictive utility of the 21-gene recurrence score for endocrine therapy has also been evaluated. A comparison of the placebo- and tamoxifen-treated patients from the NSABP B-14 trial demonstrated that the 21-gene recurrence score predicted benefit from tamoxifen in cancers with low- or intermediate-risk recurrence scores [26]. However, there was no benefit from the use of tamoxifen over placebo in cancers with high-risk recurrence scores. To date, this intriguing data has not been prospectively confirmed, and thus the 21-gene recurrence score is not used to avoid endocrine therapy.

The 21-gene recurrence score is primarily used by oncologists to aid in decision-making regarding adjuvant chemotherapy in patients with node-negative and node-positive (up to 3 positive lymph nodes), HR-positive/HER2-negative breast cancers. The predictive utility of the 21-gene recurrence score for adjuvant chemotherapy was initially tested using tumor samples from the NSABP B-20 study. This study initially compared adjuvant tamoxifen alone with tamoxifen plus chemotherapy in patients with node-negative, HR-positive tumors. The prospective-retrospective biomarker analysis showed that the patients with high-risk 21-gene recurrence scores benefited from the addition of chemotherapy, whereas those with low- or intermediate-risk did not have an improved freedom from distant recurrence with chemotherapy [27]. Similarly, an analysis from the prospective phase 3 Southwest Oncology Group (SWOG) 8814 trial comparing tamoxifen to tamoxifen with chemotherapy showed that for node-positive tumors, chemotherapy benefit was only seen in those with high 21-gene recurrence scores [24].

Prospective studies are now starting to report results regarding the predictive role of the 21-gene recurrence score. The TAILORx (Trial Assigning Individualized Options for Treatment) trial includes women with...
node-negative, HR-positive and HER2-negative tumors measuring 0.6 to 5 cm. All patients were treated with standard of care endocrine therapy for at least 5 years. Chemotherapy was determined based on the 21-gene recurrence score results on the primary tumor. The 21-gene recurrence score cutoffs were changed to low (0–10), intermediate (11–25), and high (≥ 26). Patients with scores of 26 or higher were treated with chemo-therapy, and those with intermediate scores were randomly assigned to chemotherapy or no chemotherapy; results from this cohort are still pending. However, excellent breast cancer outcomes with endocrine therapy alone were reported from the 1626 (15.9% of total cohort) prospectively followed patients with low-recurrence score tumors. The 5-year invasive disease-free survival was 93.8%, with overall survival of 98% [28]. Given that 5 years is appropriate follow-up to see any chemotherapy benefit, this data supports the recommendation for no chemotherapy in this cohort of patients with very low 21-gene recurrence scores.

The RxPONDER (Rx for Positive Node, Endocrine Responsive Breast Cancer) trial is evaluating women with 1 to 3 node-positive, HR-positive, HER2-negative tumors. In this trial, patients with 21-gene recurrence scores of 0 to 25 were assigned to adjuvant chemotherapy or none. Those with scores of 26 or higher were assigned to chemotherapy. All patients received standard adjuvant endocrine therapy. This study has completed accrual and results are pending. Of note, TAILORx and RxPONDER did not investigate the potential lack of benefit of endocrine therapy in cancers with high recurrence scores. Furthermore, despite data suggesting that chemotherapy may not even benefit women with 4 or more nodes involved but who have a low recurrence score [24], due to the lack of prospective data in this cohort and the quite high risk for distant recurrence, chemotherapy continues to be the standard of care for these patients.

**PAM50 (Breast Cancer Prognostic Gene Signature)**

Using microarray and quantitative reverse transcriptase PCR (RT-PCR) on formalin-fixed paraffin-embedded (FFPE) tissues, the Breast Cancer Prognostic Gene Signature (PAM50) assay was initially developed to identify intrinsic breast cancer subtypes, including luminal A, luminal B, HER2-enriched, and basal-like [7,29]. Based on the prediction analysis of microarray (PAM) method, the assay measures the expression levels of 50 genes, provides a risk category (low, intermediate, and high), and generates a numerical risk of recurrence score (ROR). The intrinsic subtype and ROR have been shown to add significant prognostic value to the clinicopathological characteristics of tumors. Clinical validity of PAM50 was evaluated in postmenopausal women with HR-positive, early-stage breast cancer treated in the prospective ATAC and ABCSG-8 (Austrian Breast and Colorectal Cancer Study Group 8) trials [30,31]. In 1017 patients with ER-positive breast cancer treated with anastrozole or tamoxifen in the ATAC trial, ROR added significant prognostic information beyond the clinical treatment score (integrated prognostic information from nodal status, tumor size, histopathologic grade, age, and anastrozole or tamoxifen treatment) in all patients. Also, compared with the 21-gene recurrence score, ROR provided more prognostic information in ER-positive, node-negative disease and better differentiation of intermediate- and higher-risk groups. Fewer patients were categorized as intermediate risk by ROR and more as high risk, which could reduce the uncertainty in the estimate of clinical benefit from chemotherapy [30]. The clinical utility of PAM50 as a prognostic model was also validated in 1478 postmenopausal women with ER-positive early-stage breast cancer enrolled in the ABCSG-8 trial. In this study, ROR assigned 47% of patients with node-negative disease to the low-risk category. In this low-risk group, the 10-year metastasis risk was less than 3.5%, indicating lack of benefit from additional chemotherapy [31]. A key limitation of the PAM50 is the lack of any prospective studies with this assay.

PAM50 has been designed to be carried out in any qualified pathology laboratory. Moreover, the ROR score provides additional prognostic information about risk of late recurrence, which will be discussed in the next section.

**70-Gene Breast Cancer Recurrence Assay (MammaPrint)**

MammaPrint is a 70-gene assay that was initially developed using an unsupervised, hierarchical clustering algorithm on whole-genome expression arrays with early-stage breast cancer. Among 295 consecutive patients who had MammaPrint testing, those classified with a good-prognosis tumor signature (n = 115) had an excellent 10-year survival rate (94.5%) compared to those with a poor-prognosis signature (54.5%), and the signature remained prognostic upon multivariate analysis [32]. Subsequently, a pooled analysis comparing outcomes by MammaPrint score in patients with node-negative or 1 to 3 node-positive breast cancers treated as per discretion of their medical team with either adjuvant chemotherapy plus endocrine therapy or endocrine therapy alone reported that
only those patients with a high-risk score benefited from chemotherapy [33]. Recently, a prospective phase 3 study (MINDACT [Microarray In Node negative Disease may Avoid ChemoTherapy]) evaluating the utility of MammaPrint for adjuvant chemotherapy decision-making reported results [34]. In this study, 6693 women with early-stage breast cancer were assessed by clinical risk and genomic risk using MammaPrint. Those with low clinical and genomic risk did not receive chemotherapy, while those with high clinical and genomic risk all received chemotherapy. The primary goal of the study was to assess whether forgoing chemotherapy would be associated with a low rate of recurrence in those patients with a low-risk prognostic MammaPrint signature but high clinical risk. A total of 1550 patients (23.2%) were in the discordant group, and the majority of these patients had HR-positive disease (98.1%). Without chemotherapy, the rate of survival without distant metastasis at 5 years in this group was 94.7% (95% confidence interval [CI] 92.5% to 96.2%), which met the primary endpoint. Of note, initially, MammaPrint was only available for fresh tissue analysis, but recent advances in RNA processing now allow for this analysis on FFPE tissue [35].

Summary
These genomic and biomarker assays can identify different subsets of HR-positive breast cancers, including those patients who have tumors with an excellent prognosis with endocrine therapies alone. Thus, we now have the tools to help avoid the toxicities of chemotherapy in many women with early-stage breast cancer. A summary of the genomic tests available is shown in Table 1.

Case Continued
The patient undergoes 21-gene recurrence score testing, which shows a low recurrence score of 10, estimating the 10-year risk of distant recurrence to be approximately 7% with 5 years of tamoxifen. Chemotherapy is not recommended. The patient completes adjuvant whole breast radiation therapy, and then, based on data supporting AIs over tamoxifen in postmenopausal women, she is started on anastrozole [36]. She initially experiences mild side effects from treatment, including fatigue, arthralgia, and vaginal dryness, but her symptoms are able to be managed. As she approaches 5 years of adjuvant endocrine therapy with anastrozole, she is struggling with rotator cuff injury and is anxious about recurrence, but has no evidence of recurrent cancer. Her bone density scan in the beginning of her fourth year of therapy shows a decrease in bone mineral density, with the lowest T score of −1.5 at the left femoral neck, consistent with osteopenia. She has been treated with calcium and vitamin D supplements.

• How long should this patient continue treatment with anastrozole?

The risk for recurrence is highest during the first 5 years after diagnosis for all patients with early breast cancer [37]. Although HR-positive breast cancers have a better prognosis than HR-negative disease, the pattern of recurrence is different between the 2 groups, and it is estimated that approximately half of the recurrences among patients with HR-positive early breast cancer occur after the first 5 years from diagnosis. Annualized hazard of recurrence in HR-positive breast cancer has been shown to remain elevated and fairly stable beyond 10 years, even for those with low tumor burden and node-negative disease [38]. Prospective trials showed that for women with HR-positive early breast cancer, 5 years of adjuvant tamoxifen could substantially reduce recurrence rates and improve survival, and this became the standard of care [39]. AIs are considered the standard of care for adjuvant endocrine therapy in most postmenopausal women, as they result in a significantly lower recurrence rate compared with tamoxifen, either as initial adjuvant therapy or sequentially following 2 to 3 years of tamoxifen [40].

Due to the risk for later recurrences with HR-positive breast cancer, more patients and oncologists are considering extended endocrine therapy. This is based on results from the ATLAS (Adjuvant Tamoxifen: Longer Against Shorter) and aTTOM (Adjuvant Tamoxifen–To Offer More?) studies (Table 2), both of which showed that women with HR-positive breast cancer who continued tamoxifen for 10 years had a lower late recurrence rate and a lower breast cancer mortality rate compared with those who stopped at 5 years [41,42]. Furthermore, the NCIC MA.17 trial evaluated extended endocrine therapy in postmenopausal women with 5 years of letrozole following 5 years of tamoxifen. Letrozole was shown to improve both disease-free and distant disease–free survival. The overall survival benefit was limited to patients with node-positive disease [43].

However, extending AI therapy from 5 years to 10 years is not clearly beneficial. In the MA.17R trial,
although longer AI therapy resulted in significantly better disease-free survival (95% versus 91%, hazard ratio 0.66; \( P = 0.01 \)), this was primarily due to a lower incidence of contralateral breast cancer in those taking the AI compared with placebo. The distant recurrence risks were similar and low (4.4% versus 5.5%), and there was no overall survival difference [2]. Also, the NSABP B-42 study, which was presented at the 2016 San Antonio Breast Cancer Symposium, did not meet its predefined endpoint for benefit from extending adjuvant AI therapy with letrozole beyond 5 years [3]. Thus, the absolute benefit from extended endocrine therapy has been modest across these studies. Although endocrine therapy is considered relatively safe and well tolerated, side effects can be significant and even associated with morbidity. Ideally, extended endocrine therapy should be offered to the subset of patients who would benefit the most. Several geno-mic diagnostic assays, including the EndoPredict test, PAM50, and the Breast Cancer Index (BCI) tests, specifically assess the risk for late recurrence in HR-positive cancers.

### Tests for Assessing Risk for Late Recurrence PAM50

Studies suggest that the ROR score also has value in predicting late recurrences. Analysis of data in patients...
enrolled in the ABCSG-8 trial showed that ROR could identify patients with endocrine-sensitive disease who are at low risk for late relapse and could be spared from unwanted toxicities of extended endocrine therapies. In 1246 ABCSG-8 patients between years 5 and 15, the PAM50 ROR demonstrated an absolute risk of distant recurrence of 2.4% in the low-risk group, as compared with 17.5% in the high-risk group [44]. Also, a combined analysis of patients from both the ATAC and ABCSG-8 trials demonstrated the utility of ROR in identifying this subgroup of patients with low risk for late relapse [45].

**EndoPredict**

EndoPredict (EP) is another quantitative RT-PCR–based assay which uses FFPE tissues to calculate a risk score based on 8 cancer-related and 3 reference genes. The score is combined with clinicopathological factors including tumor size and nodal status to make a comprehensive risk score (EPclin). EPclin is used to dichotomize patients into EP low- and EP high-risk groups. EP has been validated in 2 cohorts of patients enrolled in separate randomized studies, ABCSG-6 and ABCSG-8. EP provided prognostic information beyond clinicopathological variables to predict distant recurrence in patients with HR-positive, HER2-negative early breast cancer [46]. More important, EP has been shown to predict early (years 0–5) versus late (> 5 years after diagnosis) recurrences and identify a low-risk subset of patients who would not be expected to benefit from further treatment beyond 5 years of endocrine therapy [47]. Recently, EP and EPclin were compared with the 21-gene (Oncotype DX) recurrence score in a patient population from the TransATAC study. Both EP and EPclin provided more prognostic information compared to the 21-gene recurrence score and identified early and late relapse events [48]. EndoPredict is the first multi-gene expression assay that could be routinely performed in decentral molecular pathological laboratories with a short turnaround time [49].

**Breast Cancer Index**

The BCI is a RT-PCR–based gene expression assay that consists of 2 gene expression biomarkers: molecular grade index (MGI) and \( \text{HOXB13/IL17BR} \) (H/I). The BCI was developed as a prognostic test to assess risk for breast cancer recurrence using a cohort of ER-positive patients \( n = 588 \) treated with adjuvant tamoxifen versus observation from the prospective randomized Stockholm trial [50]. In this blinded retrospective study, H/I and MGI were measured and a continuous risk model (BCI) was developed in the tamoxifen-treated group. More than

### Table 2. Extended Endocrine Therapy Studies for HR-Positive Breast Cancers

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment Arms</th>
<th>No. of Patients</th>
<th>BrCa Outcomes</th>
<th>Hazard Ratio (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extension with tamoxifen after completing 5 years of tamoxifen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATLAS [41]</td>
<td>Tamoxifen vs observation</td>
<td>6846 (HR+)</td>
<td>Recurrence years 5–14: 21.4% vs 25.1%</td>
<td>0.84 (( P &lt; 0.002 ))</td>
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<td></td>
<td></td>
<td></td>
<td>BrCa mortality years 5–14: 12.2% vs 15%</td>
<td>( P &lt; 0.01^* )</td>
</tr>
<tr>
<td>aTTom [42]</td>
<td>Tamoxifen vs observation</td>
<td>6953 (HR+ 2755, unknown 4198)</td>
<td>Recurrence: 28% vs 32%</td>
<td>0.85 (( P = 0.003 ))</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BrCa mortality: 21% vs 24%</td>
<td>0.88 (( P = 0.06 ))</td>
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<tr>
<td>Extension with an AI after completing 5 years of tamoxifen</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>MA.17 [43]</td>
<td>Letrozole vs placebo</td>
<td>5187</td>
<td>DFS 94.4% vs 89.8%</td>
<td>0.58 (( P &lt; 0.001 ))</td>
</tr>
<tr>
<td>NSABP B-33 [57]</td>
<td>Exemestane vs placebo</td>
<td>1598</td>
<td>DFS 91% vs 89%</td>
<td>0.68 (( P = 0.07 ))</td>
</tr>
<tr>
<td>Extension with an AI after completing 5 years of an AI (MA.17R) or sequential tamoxifen (&lt; 3 yr) then AI (B-42)</td>
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<tr>
<td>MA.17R [2]</td>
<td>Letrozole vs placebo</td>
<td>1918</td>
<td>DFS 95% vs 91%</td>
<td>0.66 (( P = 0.01 ))</td>
</tr>
<tr>
<td>NSABP B-42 [3]</td>
<td>Letrozole vs placebo</td>
<td>3966</td>
<td>DFS 84.5% vs 81.3%</td>
<td>0.85 (( P = 0.048^\dagger ))</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS 92.3% vs 91.8%</td>
<td>1.15 (( P = 0.22 ))</td>
</tr>
</tbody>
</table>

*Hazard ratio not reported.

\( P \) value did not reach prespecified statistical significance level of 0.0418.

AI = aromatase inhibitor; BrCa = breast cancer; DFS = disease-free survival; HR+ = hormone-receptor positive; OS = overall survival.
50% of the patients in this group were classified as having a low risk of recurrence. The rate of distant recurrence or death in this low-risk group at 10 years was less than 3%. The performance of the BCI model was then tested in the untreated arm of the Stockholm trial. In the untreated arm, BCI classified 53%, 27%, and 20% of patients as low, intermediate, and high risk, respectively. The rate of distant metastasis at 10 years in these risk groups was 8.3% (95% CI 4.7% to 14.4%), 22.9% (95% CI 14.5% to 35.2%), and 28.5% (95% CI 17.9% to 43.6%), respectively, and the rate of breast cancer–specific mortality was 5.1% (95% CI 1.3% to 8.7%), 19.8% (95% CI 10.0% to 28.6%), and 28.8% (95% CI 15.3% to 40.2%) [50].

The prognostic and predictive values of the BCI have been validated in other large, randomized studies and in patients with both node-negative and node-positive disease [51,52]. The predictive value of the endocrine-response biomarker, the H/I ratio, has been demonstrated in randomized studies. In the MA.17 trial, a high H/I ratio was associated with increased risk for late recurrence in the absence of letrozole. However, extended endocrine therapy with letrozole in patients with high H/I ratios predicted benefit from therapy and decreased the probability of late disease recurrence [53]. BCI was also compared to IHC4 and the 21-gene recurrence score in the TransATAC study and was the only test to show prognostic significance for both early (0–5 years) and late (5–10 year) recurrence [54].

The impact of the BCI results on physicians’ recommendations for extended endocrine therapy was assessed by a prospective study. This study showed that the test result had a significant effect on both physician treatment recommendation and patient satisfaction. BCI testing resulted in a change in physician recommendations for extended endocrine therapy, with an overall decrease in recommendations for extended endocrine therapy from 74% to 54%. Knowledge of the test result also led to improved patient satisfaction and decreased anxiety [55].

Summary
Due to the risk for late recurrence, extended endocrine therapy is being recommended for many patients with HR-positive breast cancers. Multiple genomic assays are being developed to better understand an individual’s risk for late recurrence and the potential for benefit from extended endocrine therapies. However, none of the assays have been validated in prospective randomized studies. Further validation is needed prior to routine use of these assays.

Case Continued
A BCI test is done and the result shows 4.3% BCI low-risk category in years 5–10; low likelihood of benefit from extended endocrine therapy. After discussing the results of the BCI test in the context of no survival benefit from extending AIs beyond 5 years, both the patient and her oncologist feel comfortable with discontinuing endocrine therapy at the end of 5 years.

Conclusion
Reduction in breast cancer mortality is mainly the result of improved systemic treatments. With advances in breast cancer screening tools in recent years, the rate of cancer detection has increased. This has raised concerns regarding overdiagnosis. To prevent unwanted toxicities associated with overtreatment, better treatment decision tools are needed. Several genomic assays are currently available and widely used to provide prognostic and predictive information and aid in decisions regarding appropriate use of adjuvant chemotherapy in HR-positive/HER2-negative early-stage breast cancer. Ongoing studies are refining the cutoffs for these assays and expanding the applicability to node-positive breast cancers. Furthermore, with several studies now showing benefit from the use of extended endocrine therapy, some of these assays may be able to identify the subset of patients who are at increased risk for late recurrence and who might benefit from extended endocrine therapy. Advances in molecular testing has enabled clinicians to offer more personalized treatments to their patients, improve patient’s compliance, and decrease anxiety and conflict associated with management decisions. Although small numbers of patients with HER2-positive and triple negative breast cancers were also included in some of these studies, use of genomic assays in this subset of patients is very limited and currently not recommended.

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GENOMIC TESTING IN EARLY BREAST CANCER


