Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer

Policy #  00211
Original Effective Date:  03/01/2007
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider the use of the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (i.e., Oncotype DX®) to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy in women with primary, invasive breast cancer to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility for the use of 21-gene RT-PCR assay (i.e., Oncotype DX) to determine recurrence risk for deciding whether or not to undergo adjuvant chemotherapy in women with breast cancer will be considered when ALL of the following criteria are met:

- Unilateral tumor, AND
- Hormone receptor positive (i.e., estrogen receptor (ER)-positive or progesterone receptor (PR)-positive); AND
- Human epidermal growth factor receptor 2 (HER2)-negative; AND
- Tumor size 0.6–1 cm with moderate/poor differentiation or unfavorable features OR tumor size greater than 1 cm; AND
- Node negative (lymph nodes with micrometastases (less than 2 mm in size) are considered node negative for this policy statement); AND
- Who will be treated with adjuvant endocrine therapy, e.g., tamoxifen or aromatase inhibitors AND;
- When the test result will aid the patient in making the decision regarding chemotherapy (i.e., when chemotherapy is a therapeutic option); AND
- When ordered within 6 months following diagnosis, since the value of the test for making decisions regarding delayed chemotherapy is unknown.

The 21-gene RT-PCR assay Oncotype DX should only be ordered on a tissue specimen obtained during surgical removal of the tumor and after subsequent pathology examination of the tumor has been completed and determined to meet the above criteria (i.e., the test should not be ordered on a preliminary core biopsy). The test should be ordered in the context of a physician-patient discussion regarding risk preferences when the test result will aid in making decisions regarding chemotherapy.
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For patients who otherwise meet the above characteristics but who have multiple ipsilateral primary tumors, a specimen from the tumor with the most aggressive histological characteristics should be submitted for testing. It is not necessary to conduct testing on each tumor; treatment is based on the most aggressive lesion.

Based on review of available data, the Company may consider the use of EndoPredict, the Breast Cancer IndexSM, and Prosigna‡ to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy in women with primary, invasive breast cancer with the same characteristics as considered medically necessary for Oncotype DX to be eligible for coverage.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers all other indications for the 21-gene RT-PCR assay (ie, Oncotype DX), EndoPredict, the Breast Cancer IndexSM, and Prosigna, including determination of recurrence risk in invasive breast cancer patients with positive lymph nodes, patients with bilateral disease or to consider length of treatment with tamoxifen to be investigational.*

Based on review of available data, the Company considers use of a subset of genes from the 21-gene RT-PCR assay for predicting recurrence risk in patients with noninvasive ductal carcinoma in situ (DCIS) (ie, Oncotype DXDCIS) to inform treatment planning after excisional surgery to be investigational.*

Based on review of available data, the Company considers the use of 70-gene signature (MammaPrint®)† for any indication to be investigational.*

Based on review of available data, the Company considers the use of BluePrint in conjunction with MammaPrint or alone to be investigational.*

Based on review of available data, the Company considers the use of gene expression assays for quantitative assessment of ER, PR, and HER2 overexpression (eg, TargetPrint®) to be investigational.*

Based on review of available data, the Company considers the use of gene expression assays in men with breast cancer to be investigational.*

Background/Overview

An important part of treatment planning for women with breast cancer involves determining which patients could benefit from adjuvant treatments. For example, for women with early-stage, invasive breast cancer (ie, cancer extending beyond the basement membrane of the mammary ducts into adjacent tissue), adjuvant cytotoxic chemotherapy consistently provides approximately a 30% relative risk reduction in 10-year breast cancer mortality regardless of prognosis. However, the absolute benefit of chemotherapy depends on the baseline risk of recurrence. Women with the best prognosis have small tumors, are
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estrogen receptor–positive, and are lymph node–negative. These women have an approximately 15% baseline risk of recurrence; approximately 85% of these patients would be disease-free at 10 years with tamoxifen treatment alone and could avoid the toxicity of chemotherapy, if they could be accurately identified. Conventional risk classifiers (eg, Adjuvant! Online) estimate recurrence risk by considering criteria such as tumor size, type, grade, and histologic characteristics; hormone receptor status; and lymph node status. Consensus guidelines for defining receptor status exist. However, no single classifier is considered a criterion standard, and several common criteria have qualitative or subjective components that add variability to risk estimates. As a result, more patients are treated with chemotherapy than can benefit. Better predictors of baseline risk could help women’s decision making, some who may prefer to avoid chemotherapy if assured that their risk is low.

In other clinical scenarios involving breast cancer, accurate assessment of prognosis may affect the decision to offer certain treatments. Recently, several groups have identified panels of gene expression markers (“signatures”) that appear to predict the baseline risk of invasive breast cancer recurrence after surgery, radiotherapy, and endocrine therapy (for hormone receptor–positive tumors). Several gene expression tests commercially available in the United States are listed in Table 1. If these panels are more accurate risk predictors than current conventional classifiers, they could be used to aid decision making on adjuvant treatments without greatly affecting disease-free survival and overall survival (OS). This review focuses on gene expression profiling (GEP) panels that have prognostic or predictive ability in individuals with early-stage, invasive breast cancer with known estrogen receptor and progesterone receptor and human epidermal growth factor receptor (HER2) status. The proposed clinical utility of these tests varies depending on the clinical context; these specific indications are discussed in this policy:

1. Prognosis and/or prediction of treatment response in patients with node-negative, early-stage, HER2-negative invasive breast cancer who will receive adjuvant hormonal therapy for the purpose of determining whether patients can avoid adjuvant cytotoxic chemotherapy.
2. Prognosis and/or prediction of treatment response in patients with node-positive (1-3 nodes), early-stage, HER2-negative invasive breast cancer who will receive adjuvant hormonal therapy for the purpose of determining whether patients can avoid adjuvant cytotoxic chemotherapy.
3. Prognosis and/or prediction of treatment response in patients with ductal carcinoma in situ (DCIS) for the purpose of determining whether patients can avoid radiation therapy.
4. Prognosis and/or prediction of treatment response in patients with node-negative, early-stage, HER2-negative invasive breast cancer, receiving adjuvant hormonal therapy, who have survived without progression to 5 years postdiagnosis, for the purpose of determining whether patients should continue adjuvant hormonal therapy.

For each of these clinical indications, clinical trials have shown that there is some clinical benefit to receiving the additional therapy under consideration. However, each of the additional treatments has potential adverse effects. If a patient subgroup can be defined that has an extremely low risk of distant recurrence, or a subgroup can be defined that does not respond to the treatment, then the additional treatment can be forgone with little effect on cancer outcome due to the low risk of poor outcome or lack of response to treatment.
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Table 1. Gene Expression Tests Reporting Recurrence Risk for Breast Cancer Considered Herein

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncotype DX</td>
<td>Genomic Health (Redwood City, CA)</td>
<td>21-gene RT-PCR</td>
</tr>
<tr>
<td>EndoPredict</td>
<td>Sividon Diagnostics (acquired by Myriad [Salt Lake City, UT in 2016)</td>
<td>12-gene real-time RT-PCR</td>
</tr>
<tr>
<td>Breast Cancer Index</td>
<td>bioTheranostics (San Diego, CA)</td>
<td>Combines MGI and the HOXB13:IL17BR Index using RT-PCR</td>
</tr>
<tr>
<td>MammaPrint</td>
<td>Agendia (Amsterdam, The Netherlands)</td>
<td>70-gene DNA microarray</td>
</tr>
<tr>
<td>Prosigna</td>
<td>NanoString Technologies (Seattle, WA)</td>
<td>nCounter&lt;sup&gt;®&lt;/sup&gt;‡ digital analysis system based on PAM50 breast cancer intrinsic subtype classifier</td>
</tr>
</tbody>
</table>

MGI: Molecular Grade Index; PAM50: prediction analysis of microarray 50 gene set; RT-PCR: reverse transcriptase polymerase chain reaction.

Additional commercially available tests may provide some prognostic or predictive information for breast cancer. Tests intended to assess estrogen receptor, progesterone receptor, and HER2 status, such as TargetPrint (Agendia; via quantitative microarray), are outside the scope of this review. In addition, tests that do not provide a specific recurrence risk are outside the scope of this review.

Other commercially available biomarkers are designed to provide information about tumors’ molecular subtypes (ie, luminal A, luminal B, HER2 type, and basal type). Prosigna was initially offered a molecular subtype test. The BluePrint 80-gene molecular subtyping assay (Agendia) is offered in combination with MammaPrint to augment predictive data about response to chemotherapy.

Many studies have investigated individual biomarkers or combinations of biomarkers that are associated with breast cancer outcomes. Determining which studies constitute sufficient evidence that the test or biomarker is likely to be clinically useful depends on attributes of the test such as its performance and the quality of the study generating the results. Simon et al has described a framework to evaluate prognostic biomarker evidence. Study designs such as prospective clinical trials or previously conducted clinical trials with archived tumor samples constitute stronger evidence than studies with less planned and systematic patient recruitment and data collection. Randomized trials allow determination of treatment-biomarker interactions that may be clinically important. In some clinical scenarios, demonstration of a treatment-biomarker interaction is not critical, because the decision to withhold chemotherapy in a low-risk group (to avoid chemotherapy-related morbidity) does not require the presence of a biomarker-treatment interaction. The study must generate an absolute estimate of outcome in the patient group of interest that would result in a change in management (eg, withholding of chemotherapy), and the study must have sufficient precision (narrow confidence intervals). Results of the same test across studies should show consistency of results and more than 1 study demonstrating the desired result should be available. Simon has proposed that at least 2 Simon category B studies showing results consistent with clinical utility are necessary to demonstrate adequate evidence of a biomarker.

The main outcome of interest to this review is 10-year distant recurrence-free survival. Distant recurrence is a hallmark of advanced breast cancer and thus more informative of OS than disease-free survival. Disease-free survival also includes local recurrence, which has a much better treatment prognosis distant disease.
For one of the indications in this review, the main outcome of interest is 10-year distant recurrence-free survival conditional on recurrence-free survival for 5 years. There is no definitive threshold for an acceptable trade-off of distant recurrence risk for avoidance of treatment toxicity and inconvenience that is derived from empirical evidence on patient preferences. While some studies have shown that patients are willing to accept intensive chemotherapy for even a small chance of benefit, individual patients will vary in their preferences and tolerance for adverse effects.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Oncotype DX and other tests listed herein are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

In February 2007, MammaPrint (Agendia) was cleared for marketing by FDA through the 510(k) process. In January 2015, MammaPrint was cleared for marketing by FDA through the 510(k) process for use in fresh-frozen, paraffin-embedded breast cancer tissue.

In September 2013, Prosigna was cleared for marketing by FDA through the 510(k) process. FDA determined that Prosigna was substantially equivalent to MammaPrint.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**Rationale/Source**
This policy has been updated periodically with literature searches using MEDLINE. The most recent search covered the period through October 14, 2016.

**EARLY-STAGE NODE-NEGATIVE INVASIVE BREAST CANCER CONSIDERING ADJUVANT CHEMOTHERAPY**

21-Gene Assay (Oncotype DX)
We identified 4 studies meeting selection criteria. The studies derive from 3 completed randomized trials and thus are all Simon category B studies. The study by Paik et al (2006) evaluated patients from a trial in which the subjects were part of the training set used in the development of the Oncotype algorithm, so its results might be biased. The study by Tang et al (2011) represents the same results as Paik et al (2004), but categorized by the Adjuvant! Online clinical risk stratifier (see Table 2).

Across all 3 studies in which patients were solely classified by Recurrence Score (RS), the 10-year risk of distant recurrence was low in the RS low category. Ten-year distant recurrence rates were all below 10% and the upper limit of the 95% confidence intervals (CIs) were also below 10%. In the study by Tang et al (2011), which categorized patients by both clinical risk and RS category, the RS provided further risk
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stratification within clinical risk categories. The recurrence rates for each clinical risk and RS group, although they showed that each characteristic provides some predictive capability, are somewhat arbitrary because the cutoffs used to categorize clinical risk were simply based on creating classes similar in size to RS categories. Different cutoffs for the clinical risk categories would result in different recurrence rates.

A prospective trial of Oncotype DX evaluating prognosis was published by Sparano et al (2015). Although the trial only evaluated outcomes at 5 years, it is among the few Simon category A studies available. In it, women with node-negative, estrogen receptor-positive, human epidermal growth factor receptor 2 (HER2)-positive breast cancer were evaluated with Oncotype DX. Depending on the RS, women were assigned to endocrine therapy alone (low RS), randomized to adjuvant chemotherapy or no chemotherapy (middle category RS), or assigned to adjuvant chemotherapy (high RS). The published trial only reported the findings of the group at low risk of recurrence assigned to endocrine therapy. Of 10,253 subjects, 1629 patients had a RS of 0 to 10 and did not receive adjuvant chemotherapy. Note that the cutoff score of 10 is lower than that for other studies evaluating Oncotype DX and thus evaluates a group at lower predicted risk of distant recurrence than other Oncotype DX studies, which typically used a cutoff of 18. Consequently, only 15.9% of the study population was judged low risk, which is much lower than other studies. At 5 years, the distant recurrence rate was 0.7% (95% CI, 0.4% to 1.3%). Other outcomes at 5 years were rate of invasive disease-free survival (93.8%; 95% CI, 92.4% to 94.9%), rate of freedom from recurrence (98.7%; 95% CI, 97.9% to 99.2%), and overall survival (OS; 98%; 95% CI, 97.1% to 98.6%). Results from the randomized subjects in the trial are not available. The outcomes of these subjects, who were at higher predicted risk of recurrence, would demonstrate the risk of outcomes of subjects with higher scores and perhaps determine the magnitude of benefit of chemotherapy in these subjects.

Section Summary: 21-Gene Assay (Oncotype DX)

Multiple studies derived from archived samples of previously conducted randomized controlled trials (RCTs) have shown that a low recurrence score is associated with a low absolute risk of 10-year distant recurrence with an upper 95% confidence interval bound not exceeding 10% in any study. These low absolute risks would translate to small absolute benefit from adjuvant chemotherapy. In these studies, over half of patients were classified at low risk. The 2015 prospective study by Sparano et al, although reporting results only at 5 years and using a more stringent cutoff to define a low risk score, showed very low distant recurrence rates and is consistent with the previously reported studies.

Table 2. Ten-Year Distance Recurrence by Oncotype DX Risk Score Group

<table>
<thead>
<tr>
<th>Study (Source of Patients)</th>
<th>N</th>
<th>Risk Score Group by % Patients in Risk Group</th>
<th>10-Year Distant Recurrence (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Int</td>
<td>High</td>
</tr>
<tr>
<td>Paik et al (2004) (TAM arm of NSABP B-14 trial)</td>
<td>668</td>
<td>51%</td>
<td>22%</td>
</tr>
<tr>
<td>Paik et al (2006) (TAM arm of NSABP B-20 trial)</td>
<td>227</td>
<td>59%</td>
<td>20%</td>
</tr>
<tr>
<td>Buus et al (2016) (ATAC trial)</td>
<td>680</td>
<td>64%</td>
<td>27%</td>
</tr>
</tbody>
</table>
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EndoPredict

We identified 2 studies with 3 sets of findings that met selection criteria (see Table 3). The study by Filipits et al (2011) assessed patients from 2 previously conducted clinical trials. We selected the study even though it included patients with positive nodes (32% of patients) because the expected effect of inclusion of these patients is to increase the recurrence rates and result in a conservative (biased to be high) estimate of distant recurrence. Buus et al (2016) studied patients from the ATAC trial, which evaluated the efficacy and safety of anastrozole versus tamoxifen in postmenopausal women with localized breast cancer. In both studies, risk scores were defined as high and low based on a predefined cut point corresponding to a 10% risk of distant recurrence. EndoPredict provides an EP score based solely on the gene expression assay; the EPclin score incorporates the EP score and clinical data on tumor size and nodal status. Results of node-negative patients in Buus et al were only reported in supplementary materials, because the main report only focused on combined node-positive and node-negative results. Node-negative patients constituted 73% of the subjects included in Buus et al.

All 3 sets of findings showed that a low EP score is associated with a low absolute risk of 10-year distant recurrence. In 1 study the confidence interval exceeded 10%, but this was the smallest study (n=378 subjects). When the EP score incorporates tumor size and nodal status, a low EPclin score is also associated with a low absolute risk of 10-year distant recurrence. A higher proportion of subjects were classified as low risk (55%-73%) using EPclin, but the 10-year distant recurrence rates in the low-risk group were similar to the EP low-risk group. This demonstrated that EPclin discriminates outcomes better than EP. This suggests that using EPclin would result in fewer patients choosing chemotherapy than using EP alone. The inclusion of some node-positive patients in 2 of the studies should have resulted in conservative estimates of prognosis, in that outcomes in node-negative patients in the low-risk group might be even better than shown in these studies.

Section Summary: EndoPredict

Three sets of findings derived from archived samples of previously conducted RCTs have shown that a low EP or EPclin score is associated with a low absolute risk of 10-year distant recurrence with an upper 95% confidence interval bound generally below 10%, except in 1 small study. These low absolute risks would translate to small absolute benefit of adjuvant chemotherapy. In these studies, over half of the patients were classified at low risk. The EPclin score classified a higher proportion of patients as low risk than the EP score.

Table 3. Ten-Year Distance Recurrence by EndoPredict Risk Group

<table>
<thead>
<tr>
<th>Study (Source of Patients)</th>
<th>N</th>
<th>Risk Score Group by % Patients in Risk Group</th>
<th>10-Year Distant Recurrence (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tang et al (2011) (TAM arm of NSABP B-14 trial)</td>
<td>668</td>
<td>Clin low/RS low: 32% Clin low/RS int-high: 21% Clin int-high/RS low: 18% Clin int-high/RS int-high: 29%</td>
<td>5.6% (2.5% to 9%) 12.9% (7% to 19%) 8.9% (4% to 14%) 30.7% (24% to 38%)</td>
</tr>
<tr>
<td>Tang et al (2011) (TAM arm of NSABP B-14 trial)</td>
<td>668</td>
<td>Clin low/RS low: 32% Clin low/RS int-high: 21% Clin int-high/RS low: 18% Clin int-high/RS int-high: 29%</td>
<td>5.6% (2.5% to 9%) 12.9% (7% to 19%) 8.9% (4% to 14%) 30.7% (24% to 38%)</td>
</tr>
<tr>
<td>Filipits et al (2011)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buus et al (2016)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clin: Clinical; Int: intermediate; RS: Recurrence Score; TAM: tamoxifen.
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Filipits et al (2011) (ABCSG-6 trial) 378 51% 49% 55% 45% 8% (3% to 13%) 22% (15% to 29%) 4% (1% to 8%) 28% (20% to 36%)
Filipits et al (2011) (ABCSG-8 trial) 1324 48% 52% 65% 35% 6% (2% to 9%) 15% (11% to 20%) 4% (2% to 5%) 22% (15% to 29%)
Buus et al (2016) (ATAC trial) 680 43% 57% 73% 27% 3.0% (2% to 6%) 14.6% (11% to 19%) 5.9% (4% to 9%) 20.0% (15% to 27%)


a ABCSG-6 and ABCSG-8 studies included a combined 32% node-positive patients.

Breast Cancer Index
We identified 2 studies with 3 sets of findings of the Breast Cancer Index (BCI) that met selection criteria (see Table 4). Some HER2-positive patients were included in both studies, but these numbers were not stated. Sgroi et al (2013) analyzed patients receiving anastrozole or tamoxifen in the ATAC trial. This trial constitutes a Simon category B study. Two versions of the BCI score were generated in the study: the BCI-C, based on cubic combinations of the variables, and the BCI-L, based on linear combinations of the variables. The second study, by Zhang et al, reported 2 sets of findings, one set deriving from a clinical trial and another from patient registries. Patients from the registry were only included if tissue samples were available.

In all sets of findings, a BCI low-risk category classified more than half of the patients as low risk, and such patients had low risk of disease recurrence at 10 years. Sgroi et al found that the BCI-C and BCI-L showed a low risk of disease recurrence in the low-risk groups, with the confidence intervals not exceeding 10%. In the study by Zhang et al, patients in BCI low-risk categories also showed a low risk of distant disease recurrence, with confidence intervals not exceeding 10%.

Section Summary: Breast Cancer Index
Three sets of findings for the BCI showed a low risk of 10-year distant recurrence among patients classified at low risk. Two sets of findings are derived from clinical trials and are categorized as Simon category B. The findings from the multicenter registry are Simon category C.

Table 4. Ten-Year Distance Recurrence by Breast Cancer Index Risk Group

<table>
<thead>
<tr>
<th>Study (Source of Patients)</th>
<th>N</th>
<th>Risk Score Group by % Patients in Risk Group</th>
<th>10-Year Distant Recurrence (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BCI Low</td>
<td>BCI Int</td>
</tr>
<tr>
<td>Zhang et al (2013) (multi-center registry)</td>
<td>358</td>
<td>55%</td>
<td>22%</td>
</tr>
<tr>
<td>Zhang et al (2013) (Stockholm trial)</td>
<td>317</td>
<td>64%</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>58%</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BCI-L Low</td>
<td>BCI-L Int</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Low</th>
<th>Int</th>
<th>High</th>
<th>4.8%</th>
<th>18.3%</th>
<th>29.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>59%</td>
<td>25%</td>
<td>16%</td>
<td>(3.0% to 7.6%)</td>
<td>(12.7% to 25.8%)</td>
<td>(21.1% to 39.1%)</td>
</tr>
</tbody>
</table>

BCI-C: Breast Cancer Index using cubic form of variables; BCI-L: Breast Cancer Index using linear form of variables.

Subgroup not receiving chemotherapy.

70-Gene Signature (MammaPrint)

We identified 1 study of MammaPrint that met selection criteria (see Table 5). Studies not meeting selection criteria often had mixed populations, including node-positive patients, mixed node-positive and node-negative patients, or patients receiving chemotherapy. The selected study by Bueno-de-Mesquita et al (2011) also initially evaluated a mixed population, but it presented relevant subgroup results. This study sample derived from 3 separate cohorts in cancer registry studies, thus the study would be classified as Simon category C. For this evidence review, we present only the results for estrogen receptor-positive cancers. Risk groups were based on multiple clinical classification methods and the gene expression profile. Three clinical classification methods were used, and the results of any 2 clinical methods were classified as concordant low risk, discordant, and concordant high risk. Because the patterns were very similar across all 3 combinations of 2 clinical classification methods, only the results for combining Adjuvant! Online and Nottingham Prognostic Index (NPI) are presented.

Only patients with both clinical risk scores (low risk and a MammaPrint low-risk score) had a 10-year distant recurrence risk below 10%. All other combinations of clinical risk and MammaPrint risk had 10-year recurrence risks greater than 10%. This pattern would suggest that a clinical strategy of using MammaPrint only in those with 2 clinical risk scores indicating low risk would identify patients with low absolute risk of recurrence.

Table 5. Ten-Year Distance Recurrence by MammaPrint Risk Group

<table>
<thead>
<tr>
<th>Study (Source of Patients)</th>
<th>N</th>
<th>Risk Score Group by % Patients in Risk Group</th>
<th>10-Year Distant Recurrence (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bueno-de-Mesquita et al (2011) (3 combined cohorts)</td>
<td>139</td>
<td>Clin low/low MP low: 24%</td>
<td>3% (0% to 9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clin low/low MP high: 10%</td>
<td>34% (9% to 59%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clin discordant MP low: 22%</td>
<td>11% (0% to 22%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clin discordant MP high: 9%</td>
<td>31% (6% to 56%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clin high/high MP low: 9%</td>
<td>23% (0% to 46%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clin high/high MP low: 26%</td>
<td>47% (31% to 63%)</td>
</tr>
</tbody>
</table>

Clin: clinical; MP: MammaPrint.

We also present results from the recently published MINDACT trial by Cardoso et al (2016), because it represents a prospectively designed trial evaluating MammaPrint, with some additional randomized components. Currently, only 5-year results are available. In this trial, women with early-stage breast cancer were evaluated with both MammaPrint and a clinical risk estimator. Women at low risk with both methods did not receive chemotherapy. Women with discordant risks were randomized to chemotherapy or to no chemotherapy. Women at high risk with both methods received chemotherapy.

Although parts of the study are an RCT, the end point for this particular analysis was the distant recurrence rate among patients with high-risk clinical and low-risk genetic profile who did not receive chemotherapy.
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Investigators prespecified that the upper bound of the 95% confidence interval for distant recurrence was 8%, which they stated would be a sufficiently low risk that such patients could reasonably avoid chemotherapy. Declaring this to be the main end point implies a clinical strategy of using MammaPrint only in patients at high clinical risk, and deferring chemotherapy in those tested patients who have low genetic risk score. In this strategy, patients at low clinical risk are not tested with MammaPrint.

Trial entry criteria included patients with either node-positive, estrogen receptor-positive, or HER2-positive breast cancer. However, these patients constituted a minority of those in the study. The main results included these patients. The authors conducted supplemental analyses of various subgroups, including the subset who were node-negative, estrogen receptor-positive, or HER2-negative. To report results of patients most comparable to the other studies discussed herein, we abstracted the results of these supplemental analyses (see Table 6). The results are qualitatively similar to the published main results.

In the main article, the principal objective of the study was met. The group at high clinical risk and low genomic risk who did not receive chemotherapy had a distant recurrence rate of 5.3% (95% CI, 3.8% to 7.5%). In the node-negative, estrogen receptor-positive, or HER2-negative subgroup analysis, this group has a distant recurrence rate of 4.5% (95% CI, 3.8% to 8.4%). In this subgroup, the confidence interval exceeded the prespecified bound of 8%.

In the group with clinical low risk and high genomic risk, who were not considered in the main outcome, in both the main analysis and in the node-negative, estrogen receptor-positive, or HER2-negative subgroup, the results would indicate that the risk of distant recurrence is not low enough to avoid chemotherapy (main analysis distant recurrence, 5% [95% CI, 3% to 8.2%]; hazard ratio subgroup distant recurrence, 6.1% [95% CI, 3.9% to 9.4%]). In the testing strategy implied in this study, by not testing for genomic risk in the low clinical risk group, these patients would not be identified.

The groups randomized to chemotherapy showed no significant difference in 5-year distant recurrence, but the confidence intervals were wide and thus uninformative regarding whether chemotherapy is or is not beneficial in these patient groups. In the main study, the hazard ratio for chemotherapy in the high clinical risk/low genomic risk was 0.78 (95% CI, 0.5 to 1.21). The hazard ratio for chemotherapy in the low clinical risk/high genomic risk group was 1.17 (95% CI, 0.59 to 2.28).

Table 6: MINDACT Trial 5-Year Distant Recurrence for the Node-Negative, Estrogen Receptor–Positive, or HER2-Negative Subgroup

<table>
<thead>
<tr>
<th>Study (Trial)</th>
<th>N</th>
<th>Risk Score Group by % Patients in Risk Group</th>
<th>5-Year Distant Recurrence (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardoso et al (2016) (MINDACT trial)</td>
<td>4225</td>
<td>Clin low/MP low: 58%</td>
<td>2.4% (1.8% to 3.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clin low/MP high: 11%</td>
<td>6.1% (3.9% to 9.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clin high/MP low: 17%</td>
<td>4.5% (2.4% to 8.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clin high/MP high: 14%</td>
<td>9.1% (6.8% to 12%)</td>
</tr>
</tbody>
</table>

Clin: clinical; HER2: human epidermal growth factor receptor 2; MP: MammaPrint.

a All clin high/MP high subjects received chemotherapy
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Section Summary: 70-Gene Signature (MammaPrint)
One Simon category C study has evaluated MammaPrint and provided 10-year distant recurrence outcomes. In that study, only subjects with both low clinical risk and low gene profiling risk have absolute rates of recurrence low enough to consider deferring chemotherapy. The sample size for this result was small, and the proportion of patients identified at low risk was a small proportion (24%) of the study sample. The Simon category A study of MammaPrint currently only provides 5-year distant recurrence outcomes. The principal result of the clinical high-risk plus MammaPrint low-risk patients may not be a low enough risk to defer chemotherapy because these 5-year recurrence rates will probably be much higher at 10 years. A group that may ultimately be identified as having sufficiently low absolute risk (but was not highlighted in the published study) is the group at clinical low risk and MammaPrint low risk, which at 5 years had a low absolute risk of distant recurrence of 2.4%.

Prosigna
We identified 2 sets of findings that met selection criteria. All studies are classed as Simon category B. However, the distant recurrence rates from the study by Dowsett et al (2013) were not directly reported in the published article so rates cited in Table 7 are based on visual estimates of the graphic results.17 Confidence intervals are not available either. Both studies reported distant recurrence rates below 5%, with the confidence intervals for the 2 studies reporting them not exceeding 8%. In the 2 studies reporting the proportion of patients classified as low risk, more than 47% of patients were classified at low risk.

Section Summary: Prosigna
Two category Simon B studies of Prosigna have shown absolute risks of 10-year distant recurrence that are sufficiently low for consideration of avoiding adjuvant chemotherapy. However, these results should be viewed cautiously because they may be due to variation in the tests used in these different studies.

Table 7. Ten-Year Distance Recurrence by Prosigna Recurrence Score Group

<table>
<thead>
<tr>
<th>Study (Trial)</th>
<th>N</th>
<th>Risk Score Group (%) Patients in Risk Group</th>
<th>10-Year Distant Recurrence (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low</td>
<td>Int</td>
</tr>
<tr>
<td>Gnant et al (2014)</td>
<td>1047</td>
<td>47%</td>
<td>32%</td>
</tr>
<tr>
<td>(ABCSD-8 trial)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dowsett et al (2013)</td>
<td>739</td>
<td>59%</td>
<td>33%</td>
</tr>
<tr>
<td>(ATAC trial)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Int: intermediate; NR: not reported.

EARLY-STAGE NODE-POSITIVE INVASIVE BREAST CANCER CONSIDERING ADJUVANT CHEMOTHERAPY
21-Gene Assay (Oncotype DX)
Albain et al (2010) evaluated samples from the Southwest Oncology Group Trial 8814, in which randomized node-positive, estrogen receptor-positive patients treated with tamoxifen for 5 years were compared with those treated with cyclophosphamide, doxorubicin, fluorouracil (CAF) chemotherapy followed by tamoxifen (CAF-T) for 5 years. Samples were available for determination of the RS for 41% (n=148) and 39% (n=219) of the trial arms, respectively.
In this trial, 10-year DFS and OS outcomes in the tamoxifen study arm differed by RS risk category (p=0.017 and 0.003, respectively), suggesting that the RS is prognostic. When the 2 treatment arms were compared within RS risk categories, only patients in the high RS category significantly benefited from the addition of CAF to tamoxifen (10-year DFS, 42% [tamoxifen] vs 55% [CAF-T], p=0.033; 10-year OS, 51% [tamoxifen] vs 68% [CAF-T]; p=0.027), suggesting that the RS is also predictive of response to chemotherapy. DFS at 10 years in the low-risk group receiving tamoxifen was 60%.

A multivariate analysis of RS tamoxifen interaction for the outcome of DFS, adjusted for the number of positive nodes, was significant for the first 5 years of follow-up (p=0.029) and remained significant after adjusting for age, race, tumor size, progesterone receptor status, grade, p53 status, and HER2 status. However, the interaction was not significant (p=0.15) after adjusting for estrogen receptor level (ER gene expression is a component of the 21-gene profile). Interaction results were similar for OS.

Dowsett et al (2010) included a separate evaluation of node-positive patients in their examination of ATAC trial samples. Of 306 node-positive patients, 243 had 1 to 3 involved nodes, and 63 had 4 or more; these were not evaluated separately. However, there is a graphic showing outcomes of patients with 1 to 3 nodes and 4 or more nodes showing that outcomes of patients with 1 to 3 nodes are intermediate between patients without nodes and those with 4 or more nodes. Rates of distant recurrence at 9 years were 17% (95% CI, 12% to 24%), 28% (95% CI, 20% to 39%), and 49% (95% CI, 35% to 64%), in low, intermediate, and high RS risk groups, respectively. It is unclear that the risk of distant recurrence in low-risk RS patients would be sufficiently low to forget chemotherapy. The authors noted that their study "did not directly evaluate the value of RS in predicting the benefit of chemotherapy.”

Goldstein et al (2008) evaluated samples from the Eastern Cooperative Oncology Group E2197 trial, which included patients with 0 to 3 positive lymph nodes and operable tumor greater than 1 cm. Patients were randomly assigned to doxorubicin plus cyclophosphamide or docetaxel plus 5 years of endocrine therapy; outcomes did not differ significantly across the study arms. A case-control study of samples from this trial found that low-risk RS patients with 0 to 1 positive nodes had a recurrence risk of 3.3% (95% CI, 2.2% to 5%), and low-risk patients with 2 to 3 positive nodes had a recurrence risk of 7.9% (95% CI, 4.3% to 14.1%). RS also was a significant predictor of risk regardless of nodal status.

The study by Gluz et al (2016) was a prospectively designed to evaluate outcomes of patients selected to avoid chemotherapy based on RS. This trial included patients with positive nodes. The sample size of patients with 1 to 3 positive nodes is 930, but the size of the sample followed for long-term outcome is uncertain. Chemotherapy was deferred in patients who had an RS less than 12. The 3-year DFS for patients with 1 to 3 positive nodes with an RS less than 12 was 97.9%. The 3-year DFS for patients with negative nodes was 98.6%. Although DFS was similar between node-positive and node-negative patients at 3 years, the number of events was very small at this time point (8 total events) and follow-up is still early.

Although the previously described studies all demonstrate that the RS stratifies patients with positive nodes into categories of patients with different risks of recurrence, the rates of recurrence shown in node-positive patients are consistently higher than patients without positive nodes. The 1 study showing similar risks of
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recurrence had low number of events and reported outcomes at 3 years. It is uncertain whether the risk of recurrent disease is low enough to consider avoiding chemotherapy.

Chang et al (2008) reported that in women with locally advanced breast cancer treated with neoadjuvant docetaxel (N=97), a complete response was more likely in those with a high RS (p=0.008). Gianni et al (2005) studied 93 patients with locally advanced breast cancer who received neoadjuvant taxane chemotherapy, then postsurgery treatment with cyclophosphamide, methotrexate, and fluorouracil as well as and tamoxifen (if estrogen receptor-positive). Pathologic complete response was more likely in patients with a high RS than with a low RS (p<0.01). Although this study is consistent with a differential effect of treatment, it does not rule out benefit in either high or low RS patients.

Section Summary: 21-Gene Assay (Oncotype DX)
Although studies derived from previously conducted clinical trials have indicated that Oncotype DX is prognostic of disease recurrence outcomes in node-positive patients, node-positive patients have a higher recurrence rate that node-negative patients. Studies have also suggested a treatment interaction with node status, indicating that low-risk patients benefit less from adjuvant chemotherapy. The finding of a treatment interaction may not be robust enough to appropriately defer chemotherapy in patients who have higher recurrence risks than patients with node-negative disease.

70-Gene Signature (MammaPrint)
In a study of node-positive disease, Mook et al (2009) evaluated 241 patients with 1 to 3 positive nodes and primarily estrogen receptor-positive, HER2-negative tumors treated variably. The 70-gene signature was a significant predictor of outcome. Reclassification analysis using Adjuvant! Online versus MammaPrint showed significant additional discrimination of outcomes by the gene signature, but all were confounded by heterogeneous patient treatment. This study also updated the results of 106 patients with 1 to 3 positive nodes from the validation study, reporting 10-year breast cancer–specific survival of 98% (95% CI, 94% to 100%) for good prognosis signatures and 64% (95% CI, 52% to 76%) for poor prognosis signatures (adjusted HR=3.63; 95% CI, 0.88 to 15.0; p=0.07).

The 2012 I-SPY trial evaluated 237 patients with locally advanced, lymph node–positive disease by correlating imaging and MammaPrint signatures with outcomes of pathologic complete response and recurrence-free survival. Despite having locally advanced disease, patients with low-risk profiles tended not to respond to chemotherapy and to have good short-term recurrence-free survival. Results are shown in Table 8. However, the number of low-risk patients is small and follow-up is only 3 years.

Table 8. Results of I-SPY: MammaPrint Results and Trial Outcomes

<table>
<thead>
<tr>
<th>MammaPrint Risk Category, % (N)</th>
<th>Proportion of Patients With pCR, % (n/N)</th>
<th>3-Year Recurrence-Free Survival, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low, 9% (11)</td>
<td>0% (0/11)</td>
<td>100% (11/11)</td>
</tr>
<tr>
<td>High, 91% (109)</td>
<td>24% (25/105)</td>
<td>75% (80/105)</td>
</tr>
</tbody>
</table>

pCR: pathologic complete response.
Saghatchian et al (2013) evaluated MammaPrint signatures of frozen tumor samples from patients with 4 to 9 positive lymph nodes. Approximately half the patients were estrogen receptor-positive, half were HER2-positive, and half had received adjuvant radiotherapy or chemotherapy. Seventy (40%) of 173 samples were classified as low risk by MammaPrint, and 103 (60%) were classified as high risk. With median follow-up of 8 years, 5-year breast cancer–specific survival in the low- and high-risk groups were 97% and 76%, respectively (p<0.01); 5-year distant metastasis-free survival was 87% and 63%, respectively (p=0.004).

Section Summary: 70-Gene Signature (MammaPrint)

The studies of MammaPrint assessing node-positive patients are confounded by characteristics such as HER2 status, estrogen receptor status, and receipt of adjuvant chemotherapy. Although MammaPrint tends to stratify patients into categories with different outcomes, it is not possible to determine the outcomes of untreated patients at 10 years and whether the risk of disease recurrence is low enough to consider avoidance of adjuvant chemotherapy.

EndoPredict, BCI, and Prosigna

We did not identify studies reporting relevant outcomes in node-positive study populations for the EndoPredict, BCI, or Prosigna tests.

DUCTAL CARCINOMA IN SITU CONSIDERING RADIOTHERAPY

Oncotype DX Breast DCIS Score

Ductal carcinoma in situ is breast cancer located in the lining of the mammary ducts that has not yet invaded nearby tissues. It may progress to invasive cancer if untreated. The incidence of DCIS diagnosis in the United States has increased in tandem with the widespread use of screening mammography, accounting for about 20% of all newly diagnosed invasive plus noninvasive breast tumors. Recommended treatment is lumpectomy or mastectomy with or without radiotherapy (RT); postsurgical tamoxifen treatment is recommended for estrogen receptor-positive DCIS, especially if excision alone is used. Because the overall rate of ipsilateral tumor recurrence (DCIS or invasive carcinoma) is approximately 25% at 10 years, it is believed many women are overtreated with RT. Thus, accurate prediction of recurrence risk may identify those women who may safely avoid radiation. The Oncotype DX Breast DCIS Score uses information from 12 of the 21 genes assayed in the standard Oncotype DX test for early breast cancer to predict 10-year risk of local recurrence (DCIS or invasive carcinoma). The stated purpose is to help guide treatment decision making in women with DCIS treated by local excision, with or without adjuvant tamoxifen therapy.

In a retrospective analysis of data and samples from patients in the prospective Eastern Cooperative Oncology Group E5194 study, Solin et al (2013) compared Oncotype DX Breast DCIS Score with 10-year local recurrence risk in a subset of DCIS patients treated only with surgery or with tamoxifen (n=327). Oncotype DX Breast DCIS Score was significantly associated with local recurrence outcomes (hazard ratio [HR], 2.31; 95% CI, 1.15 to 4.49; p=0.02) whether or not patients were treated with tamoxifen. The standard Oncotype DX score for early breast cancer was not associated with local recurrence. This study addressed the development of the Oncotype DX Breast DCIS Score and clinical validity (association of the test result
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with local recurrence outcomes). Whether women are better categorized as to their local recurrence risk by Oncotype DX Breast DCIS Score compared with standard clinical indicators of risk has not been addressed.

In another retrospective analysis, Rakovitch et al (2015) evaluated 571 tumor specimens with negative margins from a convenience cohort of patients with DCIS treated by breast-conserving surgery (lumpectomy) alone. Patients were drawn from a registry of 5752 women in Ontario, Canada, who were diagnosed with DCIS between 1994 and 2003. Median follow-up of the 571 women was 9.6 years. There were 100 local recurrence events, 43 were DCIS and 57 were invasive cancer. Oncotype DX Breast DCIS Score was significantly associated with local recurrence outcomes (HR=2.15; 95% CI, 1.43 to 3.22). Sixty-two percent of patients were classified as low risk, 17% as intermediate risk, and 21% as high risk. Corresponding 10-year local recurrence estimates were 13% (95% CI, 10% to 17%), 33% (95% CI, 24% to 45%), and 28% (95% CI, 20% to 38%), respectively. Corresponding 10-year estimates for DCIS recurrence (5% [95% CI, 3% to 9%]; 14% [95% CI, 8% to 24%]; 14% [95% CI, 9% to 22%], respectively) and for invasive breast cancer recurrence (8% [95% CI, 6% to 12%]; 21% [95% CI, 13% to 33%]; 16% [95% CI, 9% to 25%], respectively) were based on small numbers of events.

Section Summary: Oncotype DX Breast DCIS Score
Although the Oncotype DX Breast DCIS Score successfully stratified patients into groups with different outcomes, it is unclear whether estimated recurrence risks for patients classified as low risk are low enough or estimated with sufficient precision to meaningfully affect the decision to have or forgo RT.

MammaPrint, EndoPredict, BCI, and Prosigna
We did not identify studies evaluating the MammaPrint, EndoPredict, BCI, and Prosigna tests for patients with DCIS.

CONTINUATION OF TAMOXIFEN THERAPY BEYOND 5 YEARS
Clinical trials have shown benefits of extended tamoxifen beyond 5 years in patients with early-stage node-negative invasive breast cancer. It has been proposed that genetic expression profiles may provide stratification that would allow certain patients at low risk to avoid extended tamoxifen and its potential adverse effects.

EndoPredict
Dubsky et al (2013) analyzed late recurrences in 1702 patients from the ABCSG6 and ABCSG8 trials who were treated with 5 years of endocrine therapy. At 5 years, 998 patients were followed who had not had distant recurrence at that point in time. Patients were classified by score based solely on the gene expression profile (EP low and EP high) and by score based on clinical variables and gene expression profile (EP-clin low and EP-clin high). Between 5 and 10 years, the EP low group showed an absolute freedom of distant recurrence rate of 96.29% (95% CI, 93.5% to 99.1%). Outcomes of the EP high group were not reported. For the EP-clin low group, distant recurrence free survival was 98.2% (95% CI, 96.5% to 99.9%). For the EP-clin high group, distant recurrence free survival was 87.7% (95% CI, 82.9% to 92.5%).
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Breast Cancer Index
Sgroi et al (2013) analyzed late recurrences in patients from the ATAC trial. This trial was previously discussed in the evaluation of node-negative breast cancer. Analysis of distant recurrence between 5 and 10 years showed distant recurrence rates of 3.5% (95% CI, 2.0% to 6.1%), 13.4% (95% CI 8.5% to 20.5%), and 13.3% (95% CI, 7.4% to 23.4%), for BCI low-, intermediate, and high-risk groups, respectively. In the study by Zhang et al (2013), analysis of distant recurrence between 5 and 10 years showed distant recurrence rates of 2.8% (95% CI, 0.3% to 5.2%), 7.2% (95% CI, 0.1% to 13.8%), and 10.1% (95% CI, 0.2% to 19.1%), for BCI low-, intermediate-, and high-risk groups, respectively (findings from the Stockholm clinical trial).

Prosigna
A study by Filipits et al (2014) reported on the association of the risk of recurrence (ROR) score with late distant recurrence in the subset of patients who were disease free in the first 5 years after diagnosis. In the low ROR group, estimated distant recurrence-free survival was 97.5% (95% CI, 94.6% to 98.9%). The other ROR groups had lower distant recurrence-free survival rates (see Table 9).

Sestak et al (2013) also reported data from the ATAC trial on outcomes for patients classified by ROR contingent on being recurrence free at 5 years. Patients in the low-risk ROR score (with low vs high determined by the median value) had a distant recurrence-free survival at 10 years of approximately 96% (extrapolated from Kaplan-Meier curves) (see Table 9).

Table 9: Summary of Prosigna Studies on Late Recurrence Conditional on 5-Year Distant Recurrence-Free Survival

<table>
<thead>
<tr>
<th>Study/Trial</th>
<th>Population</th>
<th>N (Node-Negative)</th>
<th>Death/Distant Recurrence Events</th>
<th>Distant Recurrence-Free Survival (95% Confidence Interval)</th>
</tr>
</thead>
</table>
| Filipits et al (2014) ABCSG8 | Chemotherapy -untreated; only patients surviving to 5 y | 919 | 38 | 15-y; node negative (contingent on survival to 5 y):  
• Low (n=448): 97.5% (94.6% to 98.9%)  
• Intermediate (n=292): 90.0% (86.3% to 94.0%)  
• High (n=179): 85.8% (72.5% to 93%) |
| Sestak et al (2013) ATAC | Chemotherapy -untreated subset; U.K. patients | 683 | Not reported for node-negative patients | 10-y; combined node positive and negative (contingent on survival to 5 y; values estimated from Kaplan-Meier curves):  
• Low: 96%  
• High: 81% |

Oncotype DX and MammaPrint
We did not identify studies examining the Oncotype DX and MammaPrint tests for this indication.

Section Summary: Continuation of Tamoxifen Therapy Beyond 5 Years
For each of the EndoPredict, BCI, and Prosigna tests, there is at least 1 study that demonstrated each test stratified patients into groups with low and high distant recurrence risk, conditional on freedom of recurrent disease at 5 years. It is unclear what a reasonable threshold of risk would be to consider avoiding extended...
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tamoxifen treatment. Additional studies are needed to determine whether the risk of low-risk patients is sufficiently low to consider avoiding extended adjuvant endocrine therapy.

TEST COMPARISON STUDIES
Sgroi et al (2013) compared BCI and Oncotype DX in 665 lymph node–negative women receiving endocrine therapy but not chemotherapy in the ATAC trial. The distribution of patients across risk groups was similar. For patients receiving tamoxifen alone or in combination with anastrozole, 10-year distant recurrence risk estimates for the 2 tests were similar within risk groups. In the anastrozole group, BCI was a better predictor of risk: 5% of BCI low-risk patients had distant recurrence compared with 9% of Oncotype DX low-risk patients, and 22% of BCI high-risk patients had distant recurrence compared with 13% of Oncotype DX high-risk patients. Importantly, these values were reported without 95% confidence intervals; it is therefore not possible to assess the degree of overlap between risk groups.

Dowsett et al (2013) compared PAM50 ROR score with the Oncotype DX 21-gene RS and Breast IHC4. Patients had estrogen receptor–positive, primary breast disease treated with anastrozole or tamoxifen in the ATAC trial (a double-blinded, phase 3 clinical trial designed to compare the ability of anastrozole, tamoxifen, and the 2 drugs in combination to prevent breast cancer recurrence in postmenopausal women with hormone receptor-positive tumors). Lymph node–negative and –positive patients were included. Messenger RNA from 1017 patients was assessed for ROR, and likelihood ratio tests and concordance indices were used to assess the prognostic information provided beyond that of a clinical treatment score. Statistical testing of these parameters was significant and favored ROR score compared with RS. More patients were classified as high risk and fewer as intermediate risk by ROR than by RS. Prognostic information provided by ROR score and IHC4 was similar.

Hornberger et al (2012) conducted a systematic review on the clinical validity, clinical utility, change in clinical practice, and economic implications of early-stage breast cancer stratifiers. Fifty-six articles published original evidence addressing the 21-gene RS (Oncotype DX; n=31), 70-gene signature (MammaPrint; n=14), Adjuvant! Online (n=12), 5-antibody immunohistochemical (IHC) panel (Mammostrat; n=3), and 14-gene signature (BreastOncPx; n=1). Oncotype DX RS satisfied level 1 evidence for estimating DRR, OS, and response to adjuvant chemotherapy, and level 2 evidence for estimating local recurrence risk. Mammostrat and MammaPrint satisfied level 2 evidence for estimating distant recurrence risk and OS. Adjuvant! Online satisfied level 2 evidence for estimating distant recurrence risk, OS, and chemotherapy response. BreastOncPx satisfied level 3 evidence for predicting distant recurrence risk and OS. Ten studies reported changes in clinical practice patterns using Oncotype DX; overall, Oncotype DX was associated with change in treatment recommendations and/or decisions in 21% to 74% of cases.

Fan et al (2006) used 5 gene expression classifiers to evaluate a single set of samples from 295 women with stage 1 or 2 breast cancer, variable node involvement, and variable endocrine or chemotherapy treatment. The classifiers included the 21-gene RS, the 70-gene signature, the H/I ratio, and the intrinsic subtype classifier (similar to the commercially available PAM50). Most highly correlated were the 21-gene RS and the 70-gene signature, with a Cramer V of 0.6 (scale 0-1, with 1 indicating perfect agreement). More specifically, 81 (79%) of 103 samples with an RS of low or intermediate risk were classified as having
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a low-risk 70-gene profile. Restricting the analysis to 225 estrogen receptor-positive samples slightly reduced the correlation. Analysis was not further restricted to node-negative patients, the present indication for both tests.

Espinosa et al (2005) compared the 21-gene RS (Oncotype DX), the 70-gene signature (MammaPrint), and the 2-gene ratio (H/I ratio) in 153 patients with estrogen receptor-positive breast cancer treated with adjuvant tamoxifen. Sixty-two percent of patients were node-negative, and 63% were additionally treated with chemotherapy. Estimated DMFS for RS risk groups was 98% for low-risk, 81% for intermediate-risk, and 69% for high-risk patients; for the 70-gene signature, estimates were 95% for good prognosis and 66% for poor prognosis patients; and for the 2-gene ratio, estimates were 86% for favorable and 70% for unfavorable prognosis. The correlation between the 21-gene RS and the 70-gene signature was good (Cramer V=0.6). Slightly more variation in DMFS was explained by the combination of the 21-gene RS and either Adjuvant! Online (25.8±1.4) or the NPI (23.7±1.5) than by the combination of the 70-gene signature plus Adjuvant! Online (23.1±1.2) or the NPI (22.4±1.3), but differences were small and any combination was significantly better than any test or clinicopathologic classifier alone.

Two recent studies have compared Oncotype DX and other gene expression profiles. Kelly et al (2012) evaluated Oncotype DX and PAM50 in 108 cases and found good agreement between the 2 assays for high- and low-prognostic risk assignment; PAM50 assigned about half of Oncotype DX intermediate-risk patients to the PAM50 luminal A (low-risk) category. Prat et al (2012) evaluated several gene expression tests, including Oncotype DX, PAM50, and MammaPrint, in 594 cases and found all predictors were significantly correlated (Pearson r range, 0.36-0.79; p<0.001 for each comparison).

ADDITIONAL APPLICATIONS AND OTHER TESTS
Based on a study published in 2008 that compared Oncotype DX estrogen and progesterone receptor results with traditional IHC results, Genomic Health now includes quantitative estrogen and progesterone receptor component results in Oncotype DX 21-gene profile reports. The study reported 90% or better concordance between the 2 assays, but quantitative estrogen receptor by Oncotype DX was more strongly associated with disease recurrence than IHC results. However, estrogen and progesterone receptor analysis is traditionally conducted during pathology examination of all breast cancer biopsies, whereas Oncotype DX is indicated only for known estrogen receptor-positive tumors, after the pathology examination is complete, the patient meets specific criteria, and patient and physician are considering preferences for risk and chemotherapy. Thus, Oncotype DX should not be ordered as a substitute for estrogen and progesterone receptor IHC. Additionally, accepted guidelines for estrogen and progesterone receptor testing outline standards for high-quality IHC testing and do not recommend confirmatory testing; thus the 21-gene RS should not be ordered to confirm estrogen and progesterone receptor IHC results. A subsequent study by Khoury et al (2015) reported better correlation (for overall data) between IHC and Oncotype DX for progesterone receptor status (Spearman ρ=0.91) than for estrogen receptor status (Spearman ρ=0.65), but worse concordance (at various cut points) for progesterone receptor status than for estrogen receptor status (99% vs 98%, respectively).

No published literature on use of gene expression profiling in men with breast cancer was identified.
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Investigators have examined the ability of gene expression tests to provide risk information for locoregional recurrence. The reason for analyzing these tests in relation to locoregional recurrence is that they may have implications for the type and extent of initial local treatment. Drukker et al (2014) applied MammaPrint to 1053 tumor specimens from 1848 patients enrolled in 8 previous MammaPrint studies. Most patients had estrogen receptor-positive, HER2-negative disease; approximately half of patients had positive axillary lymph nodes. Most patients received RT and did not receive adjuvant chemotherapy; approximately half received adjuvant endocrine therapy. At median follow-up of 9 years, estimated 10-year locoregional recurrence risk was 13% (95% CI, 10% to 16%) for 492 patients categorized as MammaPrint high-risk versus 6% (95% CI, 4% to 9%) for 561 MammaPrint low-risk patients. This association was observed during the first 5 years after diagnosis, but not during years 5 to 10. Recurrence stratified by MammaPrint risk class was not associated with primary locoregional treatment (ie, not predictive of treatment response). Fitzal et al (2015) evaluated local recurrence using EndoPredict in breast tumor samples from 1324 patients who had participated in the ABCSG-8 trial (29% of enrolled patients), which compared adjuvant endocrine therapy regimens. Most patients had node-negative, estrogen receptor-positive disease and received breast-conserving surgery and radiotherapy; approximately half of patients received adjuvant endocrine therapy. At median follow-up of 6 years, Kaplan-Meier estimated 10-year risk of local recurrence-free survival was 96% (91% reported in the article abstract) among 683 patients classified by EndoPredict as high risk versus 99% among 641 patients classified by EndoPredict as low risk. EndoPredict risk groups were not associated with treatment outcomes.

Although the 3 gene expression tests are associated with risk of local recurrence, how these results would be used to change management, by either providing more aggressive treatment to high-risk patients, or providing less aggressive treatment to low-risk patients, is not clear.

We did not find studies of BluePrint molecular subtyping that reported directly outcomes of interest that would support the clinical utility of this test.

SUMMARY OF EVIDENCE
For all tests and all indications, relevant outcomes include disease-specific survival and changes in disease status.

Early-Stage Node-Negative Invasive Breast Cancer
Only studies presenting 10-year distant recurrence rates in node-negative women not receiving adjuvant chemotherapy were included in this part of the evidence review. In addition to negative nodes, the type of patient considered for this indication have positive hormone receptors and are human epidermal growth factor receptor 2 (HER2) negative.

21-Gene Assay (Oncotype DX)
For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the 21-gene assay (Oncotype DX), the evidence includes multiple prospective clinical trials and prospective-retrospective studies. Patients classified as low risk with Oncotype DX have a low risk of recurrence in which avoidance of adjuvant chemotherapy is
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reasonable (average risk at 10 years, 7%-9%; upper bound of the 95% confidence intervals, 11% to 15%). These results have been demonstrated with stronger study designs for evaluating biomarkers. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**EndoPredict**
For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with EndoPredict, the evidence includes 3 prospective-retrospective studies and observational studies. The studies showed that a low score was associated with a low absolute risk of 10-year distant recurrence. Over half of patients in the studies were classified at low risk. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Breast Cancer Index**
For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the Breast Cancer Index (BCI), the evidence includes findings from 2 prospective-retrospective studies and 1 registry-based observational study. The findings from the 2 prospective-retrospective studies showed that a low-risk BCI score is associated with low 10-year distant recurrence rates. The findings from the registry-based observational study also showed low 10-year distant recurrence rates. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**70-Gene Signature (MammaPrint)**
For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the 70-gene signature (MammaPrint), the evidence includes 1 study with outcomes in node-negative patients. Although the study showed a low risk of 10-year distant recurrence in not derived from high-quality data sources. A recently reported study of clinical utility only reported 5-year results and may not identify a group with sufficiently low risk. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Prosigna**
For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with Prosigna, the evidence includes 2 prospective-retrospective studies evaluating the prognostic ability of Prosigna. Both studies showed a low absolute risk of distant recurrence in patients with low risk scores. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Early-Stage Node-Positive Invasive Breast Cancer**
For this indication, Oncotype DX and MammaPrint have been evaluated.
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21-Gene Assay (Oncotype DX)
For individuals who have early-stage node-positive invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the 21-gene assay (Oncotype DX), the evidence includes clinical trials and prospective-retrospective studies. Although studies showed that Oncotype DX stratifies node-positive patients into high and low risks, it is still uncertain that the risk of disease recurrence is sufficiently low to avoid chemotherapy. Studies have suggested that treatment benefit in chemotherapy is restricted to high-risk patients. The evidence supporting this treatment interaction should be more robust to consider avoiding otherwise currently recommended treatment in patients not at low risk of recurrence. The evidence is insufficient to determine the effects of the technology on health outcomes.

70-Gene Signature (MammaPrint)
For individuals who have early-stage node-positive invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the 70-gene signature (MammaPrint), the evidence includes prospective-retrospective studies. Existing studies have not reported 10-year distant recurrence outcomes in the patients of interest. The studies are confounded by various factors (eg, receipt of treatment) or do not report the outcome of interest. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ductal Carcinoma In Situ
The Oncotype DX Breast DCIS Score is the only assay investigated for patients with ductal carcinoma in situ (DCIS).

For individuals who have DCIS considering radiotherapy who receive gene expression profiling with the Oncotype DX Breast DCIS assay, the evidence includes prospective-retrospective studies and prospective trials. Although studies have shown that the test stratifies patients into high- and low-risk groups, they have not yet demonstrated with sufficient precision that the risk of disease recurrence in patients identified with Oncotype DX Breast DCIS Score is low enough to consider changing the management of DCIS. The evidence is insufficient to determine the effects of the technology on health outcomes.

Continuation of Tamoxifen Therapy Beyond 5 Years
For this indication, EndoPredict, BCI, and Prosigna have been evaluated.

EndoPredict
For individuals who have early-stage node-negative invasive breast cancer free of distant recurrence at 5 years considering extending tamoxifen treatment who receive gene expression profiling with EndoPredict, the evidence includes 1 study of archived tissue samples from a previously conducted clinical trial. The study showed low distant recurrence rates in patients classified at low risk with the test. Further studies are necessary to reinforce this finding. It is unclear what an appropriate risk threshold is to consider avoidance of extending tamoxifen treatment. The evidence is insufficient to determine the effect of the technology on health outcomes.
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**Breast Cancer Index**

For individuals who have early-stage node-negative invasive breast cancer free of distant recurrence at 5 years considering extending tamoxifen treatment who receive gene expression profiling with BCI, the evidence includes 2 studies of archived tissue samples from previously conducted clinical trials. The study showed low distant recurrence rates in patients classified at low risk with the test. Further studies are necessary to reinforce this finding. It is unclear what an appropriate risk threshold is to consider avoidance of extending tamoxifen treatment. The evidence is insufficient to determine the effect of the technology on health outcomes.

**Prosigna**

For individuals who have early-stage node-negative invasive breast cancer free of distant recurrence at 5 years considering extending tamoxifen treatment who receive gene expression profiling with the Prosigna, the evidence includes 2 studies from previously conducted clinical trials. The studies showed low distant recurrence rates in patients classified at low risk with the test. Further studies are necessary to reinforce this finding. It is unclear what an appropriate risk threshold is to consider avoidance of extending tamoxifen treatment. The evidence is insufficient to determine the effect of the technology on health outcomes.

**BluePrint and TargetPrint**

The 80-gene expression assay BluePrint discriminates among 3 breast cancer molecular subtypes, and TargetPrint is a method to measure ER, PR, and HER2 as an alternative to immunohistochemistry and FISH. Clinical utility of BluePrint is unknown, as it is unclear how this test will add to treatment decision making using currently available, accepted methods (eg, clinical and pathologic parameters). The incremental benefit of using TargetPrint as an alternative to current standard methods of measuring ER, PR, and HER2 has not been demonstrated, nor is it included in recommendations for testing issued by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists.

**CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 1 physician specialty society and 4 academic medical centers while this policy was under review in 2008. A clear majority of the reviewers agreed with the policy conclusions.

**ONGOING AND UNPUBLISHED CLINICAL TRIALS**

Some currently unpublished trials that might influence this review are listed in Table 11.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
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<table>
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<tr>
<th>NCT00310180</th>
<th>Program for the Assessment of Clinical Cancer Tests (PACCT-1): Trial Assigning Individualized Options for Treatment: The TAILORx Trial</th>
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<tr>
<td>NCT00433589a</td>
<td>MINDACT (Microarray In Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy): A Prospective, Randomized Study Comparing the 70-Gene Signature With the Common Clinical-Pathological Criteria in Selecting Patients for Adjuvant Chemotherapy in Breast Cancer With 0 to 3 Positive Nodes</td>
<td>6600</td>
<td>Mar 2020</td>
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<tr>
<td>NCT01272037</td>
<td>A Phase III, Randomized Clinical Trial of Standard Adjuvant Endocrine Therapy +/- Chemotherapy in Patients With 1-3 Positive Nodes, Hormone Receptor-Positive and HER2-Negative Breast Cancer With Recurrence Score (RS) of 25 or Less. RxPONDER: A Clinical Trial Rx for Positive Node, Endocrine Responsive Breast Cancer</td>
<td>5000</td>
<td>Feb 2022</td>
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<tr>
<td>NCT02400190</td>
<td>The IDEA Study (Individualized Decisions for Endocrine Therapy Alone)</td>
<td>200</td>
<td>Mar 2026</td>
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NCT: national clinical trial.  
*a* Denotes industry-sponsored or cosponsored trial.

**References**

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09/06/2006 Medical Director review
09/20/2006 Medical Policy Committee approval
10/03/2007 Medical Director review
02/13/2008 Medical Director review
02/20/2008 Medical Policy Committee approval. Policy statement changed to include patient selection criteria. Added 21-gene RT-qPCR assay Oncotype DX.
02/04/2009 Medical Director review
02/19/2009 Medical Policy Committee approval. Clarified 6th and 7th criteria bullets. No change to coverage eligibility.
02/04/2010 Medical Policy Committee review
02/17/2010 Medical Policy Implementation Committee approval. No change to coverage.

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02/03/2011 Medical Policy Committee review
02/16/2011 Medical Policy Implementation Committee approval. New criteria added.
02/02/2012 Medical Policy Committee review
02/15/2012 Medical Policy Implementation Committee approval. Rationale extensively revised. Coverage eligibility unchanged.
02/07/2013 Medical Policy Committee review
02/20/2013 Medical Policy Implementation Committee approval. Added the BreastOncPx and the PAM50 Breast Cancer Intrinsic Classifier as examples of investigational gene expression assays.
04/02/2015 Medical Policy Committee review
04/20/2015 Medical Policy Implementation Committee approval. Added investigational statements to include newer assays (prosignia, BluePrint, TargetPrint, EndoPredict, MammaPrint, Mammastrat, NexCourse, Oncotype DCIS) and use of gene assays in men. Updated FDA, rationale and references.
10/08/2015 Medical Policy Committee review
10/21/2015 Medical Policy Implementation Committee approval. No change to coverage.
01/01/2016 Coding update
10/06/2016 Medical Policy Committee review
10/19/2016 Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
01/05/2017 Medical Policy Committee review
01/18/2017 Medical Policy Implementation Committee approval. EndoPredict, Breast Cancer Index and Prosigna removed from investigational statement. Coverage statement added that these tests are medically necessary for same indication as Oncotype. Coverage statement clarified with “primary, invasive” and investigational statement clarified with “length of treatment with tamoxifen.”
01/01/2018 Coding update
Next Scheduled Review Date:   01/2018

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<td></td>
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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association TEC or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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