### Policy Statement

The use of the 21-gene reverse transcriptase polymerase chain reaction (RT-PCR) assay (i.e., Oncotype DX®), as well as EndoPredict, the Breast Cancer Index™, MammaPrint®, and Prosigna, to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy may be considered **medically necessary** in women with primary, invasive breast cancer meeting **all** of the following characteristics:

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

**Note:** 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.

**Note:** Breast Cancer Index can be performed up to 5 years after the initial diagnosis since its value is in determining if an additional 5 years of endocrine therapy is indicated.

**Note:** For patients who otherwise meet the above characteristics but who have multiple ipsilateral primary tumors, a specimen from the tumor with the most aggressive histologic characteristics should be submitted for testing. It is not necessary to conduct testing on each tumor; treatment is based on the most aggressive lesion.

All other indications for the 21-gene RT-PCR assay (i.e., Oncotype DX®), EndoPredict, the Breast Cancer Index™, MammaPrint®, and Prosigna, including determination of recurrence risk in invasive breast cancer patients with positive lymph nodes, patients with bilateral disease, or to consider the length of treatment with tamoxifen, are considered **investigational**.

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 (i.e., Oncotype DX® Breast Ductal Carcinoma in Situ [DCIS] Score) to inform treatment planning after excisional surgery is considered **investigational**.

The use of BluePrint is considered **investigational**.

Use of gene expression assays in men with breast cancer is considered **investigational**.
Policy Guidelines

Unfavorable features that may prompt testing in tumors from 0.6 to 1 cm in size include the following: angiolympathic invasion, high histologic grade, or high nuclear grade.

The 21-gene reverse transcriptase polymerase chain reaction (RT-PCR) assay Oncotype DX® should not be ordered as a substitute for standard estrogen receptor, progesterone receptor, or human epidermal growth factor receptor 2 (HER2) testing.

The current American Society of Clinical Oncology and College of American Pathologists joint guidelines on HER2 testing in breast cancer (Wolff et al, 2013) has defined positive, negative, and equivocal HER2 test results, as shown in Table PG1.

Table PG1. ASCO and CAP Definitions of HER2 Test Results (Wolff et al, 2013)

<table>
<thead>
<tr>
<th>Result</th>
<th>Immunohistochemistry</th>
<th>Fluorescence In Situ Hybridization</th>
</tr>
</thead>
</table>
| Negative | 0 or 1+: No staining or faint/barely perceptible, incomplete membrane staining in any proportion of tumor cells | Ratio of HER2/CEP17<sup>a</sup> <2.0 AND Average HER2 CN <4.0 signals per cell  
Or Average HER2 CN <4.0 signals per cell<sup>b</sup> |
| Positive | 3+: At least 10% of tumor cells exhibit complete, intense, circumferential membrane staining | Ratio of HER2/CEP17 >2.0  
Or Ratio of HER2/CEP17 is <2.0 AND Average HER2 CN ≥6.0 signals per cell  
Or Average HER2 CN ≥6.0 signals per cell<sup>b</sup> |
| Equivocal| 2+: Circumferential membrane staining that is either:  
• incomplete and/or weak/moderate within >10% of tumor cells, or  
• complete and intense within ≤10% of tumor cells | Ratio of HER2/CEP17 <2.0 AND Average HER2 CN ≥4.0 and <6.0 signals per cell  
Or Average HER2 CN ≥4.0 and <6.0 signals per cell<sup>b</sup> |

ASCO: American Society of Clinical Oncology; CAP: College of American Pathologists; CEP: chromosome enumeration probe; CN: copy number; HER2: human epidermal growth factor receptor 2.  
<sup>a</sup> CEP 17 is a centromeric probe for chromosome 17 (internal control probe).  
<sup>b</sup> Signals per cell for test systems without an internal central probe.

Note: If there is an equivocal outcome for the MammaPrint® 70-Gene Breast Cancer Recurrence Assay, the determination of medical necessity is always made on a case-by-case basis.

Coding

There is a specific CPT multianalyte assay with algorithmic analysis (MAAA) code for Oncotype DX:
- **81519**: Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score

Effective July 1, 2018 there is a new CPT code specific to the Oncotype DX® Breast DCIS Score™ Test, which was produced by Genomic Health, Inc.:
- **0045U**: Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score

Effective January 1, 2018 there is a new CPT MAAA category I code specific to the Prosigna test that replaces code 0008M:
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• **81520**: Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score

**Effective January 1, 2018** there is a new CPT MAAA category I code specific to the Mammaprint® test:

• **81521**: Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis

There is a specific HCPCS code for this testing:

• **S3854**: Gene expression profiling panel for use in the management of breast cancer treatment

The other tests mentioned above would be reported with an unlisted CPT code such as the following:

• **81479**: Unlisted molecular pathology procedure
• **81599**: Unlisted multianalyte assay with algorithmic analysis

**Description**

Laboratory tests have been developed that detect the expression, via messenger RNA, of many different genes in breast tumor tissue and combine the results into a prediction of distant recurrence risk for women with early-stage breast cancer. Test results may help providers and patients decide whether to include adjuvant chemotherapy in the postsurgical management of breast cancer, to alter treatment in patients with ductal carcinoma in situ (DCIS), or to recommend extended endocrine therapy in patients who are recurrence-free at 5 years.

**Related Policies**

• N/A

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Oncotype DX® and other tests listed herein are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.
In February 2007, MammaPrint® (Agendia) was cleared for marketing by the FDA through the 510(k) process for the prediction of breast cancer metastasis. In January 2015, MammaPrint® was cleared for marketing by the 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 the FDA through the 510(k) process. Moreover, the FDA determined that Prosigna® was substantially equivalent to MammaPrint®. FDA product code: NYI.

Currently, the Breast Cancer IndexSM (Biotheranostics) and EndoPredict® (distributed by Myriad) are not FDA-approved.

**Rationale**

**Background**

**Newly Diagnosed Breast Cancer**

Most women with newly diagnosed breast cancer in the United States present with early-stage or locally advanced (i.e., nonmetastatic) disease. However, almost a third of women who are disease-free after initial local and regional treatment develop distant recurrences during follow-up.1 Current breast cancer treatment regimens involve systemic adjuvant chemotherapy, hormonal therapy, biologic therapy, or a combination, depending on patients’ baseline level of recurrence risk, hormonal markers, and risk tolerance.

Women whose tumors are positive for human epidermal growth factor receptor 2 (HER2) should receive adjuvant therapy with a HER2-directed therapy (trastuzumab with or without pertuzumab). Decision-making about adjuvant biologic therapy for women with HER2-positive cancer is not discussed here. This review focuses on 3 decision points:

1. **The decision to pursue adjuvant chemotherapy following locoregional therapy, with or without neoadjuvant chemotherapy, based on the predicted risk of recurrence, for women who are hormone receptor-positive but HER2-negative.** The use of adjuvant chemotherapy reduces the risk of breast cancer recurrence but carries risks of systemic toxicity. The risk:benefit ratio must be balanced for each patient, with a higher likelihood of net health benefits for patients with a greater baseline predicted the risk of recurrence. Some of the individual considerations are discussed below. HER2 expression independently confers an unfavorable prognosis, but assessing the independent effects of HER2 is complicated in the presence of targeted therapy; therefore, we focus specifically on patients without HER2 expression.

2. **The decision to pursue adjuvant endocrine therapy from 5 to 10 years for women who are hormone receptor-positive but HER2-negative and who have survived without recurrence for 5 years.** For patients with hormone receptor-positive tumors, the use of adjuvant endocrine therapy (tamoxifen and/or an aromatase inhibitor, with or without ovarian suppression) for 5 to 10 years after an initial diagnosis has support in clinical practice. The 2017 guidelines from the National Comprehensive Cancer Network recommend extended endocrine therapy.2 The American Society for Clinical Oncology’s 2014 focused update to its guidelines on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer have recommended 10 years of tamoxifen for pre- or perimenopausal women, and a total of seven to ten years of endocrine therapy, following 1 of 4 regimens that include tamoxifen with or without an aromatase inhibitor for postmenopausal women.3,4

3. **The decision to pursue adjuvant radiotherapy in women with ductal carcinoma in situ (DCIS).** Adjuvant radiotherapy reduces the risk of local recurrences but has not been shown to change the risk of distant recurrence or mortality. There may be a group of patients for whom the reduction in risk for local recurrence may not be large enough to justify the risks of radiotherapy.
Selection of Adjuvant Chemotherapy Based on Risk of Recurrence

An important part of treatment planning for women with breast cancer involves determining which patients could benefit from adjuvant cytotoxic chemotherapy. For example, for women with early-stage invasive breast cancer (i.e., 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 patients' baseline prognosis. However, the absolute benefit of chemotherapy depends on the underlying or baseline risk of recurrence. Women with the best prognosis have tumors that are small, early-stage, estrogen receptor-positive, and lymph node-negative (Table 1 shows recurrence risk for estrogen receptor-positive cancers for patients followed in the International Breast Cancer Study Group). Patients may have received no adjuvant treatment, or adjuvant tamoxifen and/or adjuvant chemotherapy. These women have an approximately 15% 10-year risk of recurrence with tamoxifen alone; approximately 85% of these patients could avoid the toxicity of adjuvant cytotoxic chemotherapy if they could be accurately identified. Conventional risk classifiers (e.g., Adjuvant! Online) estimate recurrence risk by considering criteria such as tumor size, type, grade, and histologic characteristics; hormone receptor status; and number of affected lymph nodes. Consensus guidelines for defining receptor status exist; however, no single classifier is considered a criterion standard. As a result, a substantial number of patients are treated with chemotherapy who fail to benefit. Better predictors of recurrence risk could help women's decision-making, some of whom may prefer to avoid chemotherapy if assured their risk is low.

Table 1. Effect of Nodal Involvement, Tumor Size, and Grade on Annual Recurrence Hazard in Estrogen Receptor-Positive Breast Cancers

<table>
<thead>
<tr>
<th>Recurrence, Hazarda (SE), %</th>
<th>0-5</th>
<th>5-10</th>
<th>10-15</th>
<th>15-20</th>
<th>20-25</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5.8</td>
<td>3.3</td>
<td>2.0</td>
<td>2.1</td>
<td>1.1</td>
</tr>
<tr>
<td>1 to 3</td>
<td>9.5</td>
<td>5.8</td>
<td>3.0</td>
<td>3.5</td>
<td>1.5</td>
</tr>
<tr>
<td>≥4</td>
<td>17.2</td>
<td>10.9</td>
<td>5.9</td>
<td>3.8</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2 cm</td>
<td>7.0</td>
<td>4.8</td>
<td>2.9</td>
<td>2.7</td>
<td>1.5</td>
</tr>
<tr>
<td>&gt;2 cm</td>
<td>12.9</td>
<td>6.1</td>
<td>2.9</td>
<td>2.7</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5.8</td>
<td>4.9</td>
<td>3.6</td>
<td>4.0</td>
<td>0.7</td>
</tr>
<tr>
<td>2</td>
<td>9.6</td>
<td>6.3</td>
<td>2.8</td>
<td>2.7</td>
<td>1.8</td>
</tr>
<tr>
<td>3</td>
<td>14.1</td>
<td>4.1</td>
<td>2.5</td>
<td>2.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Adapted from Colleoni et al (2016).1

a Number of events occurring within a time interval divided by the total years of follow-up during the interval accrued by patients at risk during the interval. Patients may have received no adjuvant treatment or have been treated with adjuvant tamoxifen and/or adjuvant chemotherapy.

Selection of Extended Endocrine Therapy

Randomized controlled trials have established that 5 years of tamoxifen improves mortality in women with hormone receptor-positive breast cancer. A 2011 individual patient data meta-analysis by the Early Breast Cancer Trialists' Collaborative Group, including 20 trials (total N=21,457 patients) found that 5 years of tamoxifen in estrogen receptor-positive disease reduced the risk of recurrences by almost 50% over 10 years on the relative scale; breast cancer mortality was decreased by 29% through 15 years.6

For patients with early-stage, invasive breast cancer that is hormone receptor-positive, the use of endocrine therapy (tamoxifen and/or an aromatase inhibitor, with or without ovarian suppression) for 5 to 10 years following initial diagnosis has support in national guidelines.2,3,7 However, the regimens available and the evidence to support them vary.
Randomized controlled trials published recently have shown that extended endocrine therapy decreases the risk of recurrence. The American Society for Clinical Oncology and the National Comprehensive Cancer Network guidelines were informed primarily by results of the ATLAS trial, which compared 5 and 10 years of tamoxifen and the subsequent aTTom trial (reported in abstract form). In both trials, in women who were hormone receptor-positive and had completed 5 years of tamoxifen, 5 years of extended tamoxifen was associated with improvements in breast cancer-specific mortality; ATLAS showed improvements in overall survival (see Table 2).

Three previously reported randomized trials of extended tamoxifen treatment had mixed findings: Tormey et al (1996; total N=194 patients), the National Surgical Adjuvant Breast and Bowel Project (Fisher et al, 2001; total N=1172 patients), and the Scottish Cancer Trials Breast Group (Stewart et al, 2001; total N=342 patients) (see Table 2).

Overall, the available trial evidence would suggest that 10 years of tamoxifen in pre- or postmenopausal women can be linked with improved survival while trials of extended aromatase inhibitors in different populations of hormone receptor-positive patients have had more mixed results.

Table 2. Randomized Trials Evaluating Adjuvant Extended Endocrine Therapies for Hormone Receptor-Positive Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparators</th>
<th>Breast Cancer-Specific Mortality</th>
<th>Overall Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Event RR (95% CI) p</td>
<td>Event RR (95% CI) p</td>
</tr>
<tr>
<td><strong>Extended tamoxifen</strong></td>
<td></td>
<td></td>
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<tr>
<td>ATLAS (2013)</td>
<td>6846 women with ER-positive, early breast cancer, after 5 y of tamoxifen</td>
<td>Continue tamoxifen to 10 y (n=3428) vs stop tamoxifen at 5 y (n=3418)</td>
<td>0.83 (0.72 to 0.96) 0.01</td>
<td>0.87 (0.78 to 0.97) 0.01</td>
</tr>
<tr>
<td>aTTom (2013)</td>
<td>6953 women with ER-positive or untested breast cancer, after 5 y of tamoxifen</td>
<td>Continue tamoxifen to 10 y (n=3468) vs stop tamoxifen at 5 y (n=3458)</td>
<td><strong>Years 5-9</strong> 1.03 (0.84 to 1.27) 0.05</td>
<td><strong>Years 5-9</strong> 1.05 (0.90 to 1.22) 0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>After year 9</strong> 0.77 (0.64 to 0.92)</td>
<td><strong>After year 9</strong> 0.86 (0.75 to 0.97)</td>
</tr>
<tr>
<td><strong>Extended aromatase inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCSG (2007)</td>
<td>856 postmenopausal women with ER- and/or PR-positive breast cancer, after 5 y of tamoxifen</td>
<td>Anastrozole for 3 y (n=386) vs no further therapy (n=466)</td>
<td>5 years 10.3% vs 11.7% 0.57</td>
<td>Event HR (95% CI) 0.89 (0.59 to 1.34)</td>
</tr>
<tr>
<td></td>
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<tr>
<td><strong>Breast Cancer-Specific Survival</strong></td>
<td></td>
<td></td>
<td>58 Months 94.4% letrozole vs 89.8% placebo Event HR 0.58 (0.45 to 0.76) &lt;0.001</td>
<td>58 Months 96% letrozole vs 94% placebo Event HR 0.76 (0.48 to 0.21) 0.25</td>
</tr>
<tr>
<td><strong>NCIC CTG MA.17 trial (2003, 2005)</strong></td>
<td>5187 postmenopausal women with ER- and/or PR-positive early breast cancer,</td>
<td>Continue letrozole to 10 y (n=2593) vs stop tamoxifen at 5 y (n=2594)</td>
<td>48 Months 94.4% letrozole vs 89.8% placebo Event HR 0.58 (0.45 to 0.76) &lt;0.001</td>
<td>48 Months 96% letrozole vs 94% placebo Event HR 0.76 (0.48 to 0.21) 0.25</td>
</tr>
</tbody>
</table>
Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparators</th>
<th>Breast Cancer−Specific Mortality</th>
<th>Overall Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP (2008)16</td>
<td>1598 post-menopausal women with ER- and/or PR-positive early breast cancer, after 5 y of tamoxifen</td>
<td>Planned comparison: 5 y exemestane vs 5 y placebo. Accrual stopped (n=1598 randomized), and crossover allowed after results of NCIC CTG available: • Exemestane: 783 randomized, 560 continued after unblinding • Placebo: 779 randomized, 334 crossed over to exemestane after unblinding</td>
<td>48 Months ITT: 91% exemestane vs 89% placebo</td>
<td>0.07 Event HR: 0.82 (0.57 to 1.19)</td>
</tr>
</tbody>
</table>

ABC SG: Austrian Breast and Colorectal Cancer Study Group; CI: confidence interval; ER: estrogen receptor; HR: hazard ratio; ITT: intention to treat; NCIC CTG: National Cancer Institute Clinical Trials Group; NSABP: National Surgical Adjuvant Breast and Bowel Project; PR: progesterone receptor; RR: rate ratio.

In addition to the trials published in full-length form, 3 trials were presented in early 2017 evaluating extended endocrine therapy in postmenopausal women (NSABP-42 [NCT00382070]: 10 years vs 5 years of letrozole; DATA [NCT00301457]: 6 years vs 3 years of anastrozole; and IDEAL [NTR3077] 10 years vs 7.5 years of letrozole) did not meet their primary end points.

Clinical Uses of Gene Expression Signatures for Breast Cancer

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 3. 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. This review focuses on gene expression profiling panels that have prognostic or predictive ability in individuals with early-stage, invasive breast cancer with known estrogen receptor and progesterone receptor and HER2 status. The proposed clinical utility of these tests varies by the clinical context; these specific indications are discussed in this review:

1. Prognosis and/or prediction of treatment response in patients with node-negative, early-stage, hormone receptor-positive, 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), hormone receptor-positive, 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 DCIS for the purpose of determining whether patients can avoid radiotherapy.

4. Prognosis and/or prediction of treatment response in patients with node-negative, early-stage, hormone receptor–positive, 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 will continue adjuvant hormonal therapy.

For each of these indications, clinical trials have shown that there is some clinical benefit to receiving the additional therapy under consideration. However, each additional treatment 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.

| Table 3. Gene Expression Tests Reporting Recurrence Risk for Breast Cancer Considered Herein |
|---------------------------------|-------------------------------------------------|
| **Test** | **Manufacturer** | **Description** |
| Oncotype DX® | Genomic Health (Redwood City, CA) | 21-gene RT-PCR; identifies 3 groups as low, intermediate, and high risk for distant recurrence |
| Breast Cancer Index® Prognostic | Biotheranostics (San Diego, CA) | Combines MGI and the HOXB13:IL17BR Index measured using RT-PCR; identifies 2 groups as low or high risk for distant recurrence |
| MammaPrint® | Agendia (Amsterdam, The Netherlands) | 70-gene DNA microarray; identifies 2 groups as low or high risk for distant recurrence |
| Prosigna® | NanoString Technologies (Seattle, WA) | Gene expression profile is assessed by the nCounter digital platform system to determine similarity with prototypic profiles of PAM50 genes for breast cancer; identifies 3 categorical ROR groups (ROR-low, ROR-intermediate, ROR-high) |

MGI: Molecular Grade Index; PAM50: prediction analysis of microarray 50-gene set; ROR: risk of relapse; RT-PCR: reverse transcriptase polymerase chain reaction; EP: expression profile.

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 (i.e., luminal A, luminal B, HER2 type, and basal type). Prosigna was initially offered as a molecular subtype test. The BluePrint® 80-gene molecular subtyping assay is offered in combination with MammaPrint to augment predictive data about response to chemotherapy.
Decision Framework for Evaluating Breast Cancer Biomarkers
Simon et al Framework
Many studies have investigated individual biomarkers or combinations of biomarkers 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 (2009) have described a framework to evaluate prognostic biomarker evidence.17 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 outcomes in the patient group of interest that would result in a change in management (e.g., withholding of chemotherapy), and the study must have sufficient precision (narrow confidence intervals). Results of the same test across studies should show the 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.17

Breast Cancer-Specific Outcomes
The main outcome of interest for this review is 10-year distant recurrence-free survival. Distant recurrence is a hallmark of advanced breast cancer and thus more informative of overall survival than disease-free survival. Disease-free survival also includes local recurrence, which has a much better treatment prognosis than distant disease. For the extended endocrine indications in this review, the main outcome of interest is 10-year distant recurrence-free survival conditional on recurrence-free survival for 5 years.

Decisions to undergo or forgo adjuvant therapy (chemotherapy or endocrine) depend on how a woman values the potential benefit of lower recurrence risk relative to the harms of treatment. The balance of benefits and harms determines the thresholds that inform decisions.18,19 Most women will accept substantial adverse events for even modest benefit. For example, Simes et al (2001) interviewed 104 Australian women with breast cancer treated with cytotoxic chemotherapy and elicited preferences to undergo chemotherapy according to probable gain in survival.20 With an expected survival of 5 years without chemotherapy, 73% said they would accept chemotherapy for an increased survival of 6 months or less; with an expected survival of 15 years, 39% would accept treatment for a gain of 6 months. Duric et al (2005) found 64% to 84% of 97 women expressing a willingness to undergo chemotherapy for a 1-year improvement in life expectancy or 3% increase in survival rates.21 About half felt a single day would justify adjuvant chemotherapy. A major difference between the 2 studies was that the chemotherapy regimen in Duric et al was less toxic. Thewes et al (2005) adopted the same approach for adjuvant endocrine therapy preferences in 102 premenopausal women with early-stage breast cancers.22 Among women having a baseline life expectancy of 5 years, 61% said they would accept endocrine therapy for a 6-month increase in life expectancy and 79% for 1 year; rates were similar if the baseline life expectancy was 15 years. These proportions are close to those for adjuvant chemotherapy found by Duric.

How these estimates correspond to the distant recurrence rates reported in prognostic studies is imprecise, but Henderson (2015) has suggested that below a recurrence threshold of 10% many patients will not elect adjuvant chemotherapy owing to the small absolute benefit.23 He also noted that a majority of those patients are older with small node-negative tumors. That interpretation is consistent with a recent study of 81 women by Hamelinck et al (2016) who found that 78% of women ages 40 to 49 years, 88% ages 50 to 59, 59% ages 60 to 69, and 40% age 70 or
older would accept adjuvant chemotherapy for a 0% to 10% absolute decrease in recurrence risk (see Table 4). There was a wide range of minimally required absolute benefits, with the majority accepting chemotherapy for an absolute benefit of 1% to 5%. At a given age range, fewer women expressed a willingness to accept adjuvant endocrine therapy than chemotherapy for a given mortality benefit.

### Table 4. Patient Preferences for Undergoing Adjuvant Therapy for <10% Reduction in Recurrence Risk

<table>
<thead>
<tr>
<th>Age Range, y</th>
<th>Proportion That Would Accept 1% to 10% Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chemotherapy, %</td>
</tr>
<tr>
<td>40-49</td>
<td>78</td>
</tr>
<tr>
<td>50-59</td>
<td>88</td>
</tr>
<tr>
<td>60-69</td>
<td>59</td>
</tr>
<tr>
<td>≥70</td>
<td>40</td>
</tr>
</tbody>
</table>

Adapted from Hamelinck et al (2016).24

### Literature Review

The most recent literature update for all indications was performed through September 11, 2017 (see Appendix Table 1 for genetic testing categories).

Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present (or in excluding a variant that is absent); (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

The following is a summary of the key literature.

### Assays of Genetic Expression in Tumor Tissue

#### Clinical Context and Test Purpose

The purpose of assays of genetic expression in tumor tissue in patients with early-stage node-negative or node-positive invasive breast cancer considering adjuvant chemotherapy; in patients with ductal carcinoma in situ (DCIS) considering radiotherapy; and in patients with early-stage node-negative invasive breast cancer, recurrence-free at 5 years considering extended endocrine therapy, is to determine risk of recurrence, which informs decisions about potential breast cancer treatment.

The question addressed in this evidence review is: Does the use of assays of genetic expression in tumor tissue improve the net health outcome in individuals with breast cancer?

The following PICOTS were used to select literature to inform this review.

#### Patients

The populations of interest include: patients with early-stage node-negative or node-positive invasive breast cancer considering adjuvant chemotherapy; patients with DCIS considering radiotherapy; and patients with early-stage node-negative invasive breast cancer, recurrence-free at 5 years considering extended endocrine therapy.

#### Interventions

The interventions of interest are assays of genetic expression in tumor tissue (Oncotype DX, EndoPredict, Breast Cancer Index [BCI], MammaPrint, Prosigna).

#### Comparators

The comparators of interest for all assays are clinical risk prediction algorithms.
Outcomes
Outcomes of interest for all assays are disease-specific survival and change in disease status. If patients with early-stage invasive breast cancer are classified as low risk for distant recurrence, patients may be able to forgo adjuvant chemotherapy safely.

If patients with DCIS are classified as low risk for distant recurrence, they may be able to safely forgo radiotherapy.

If patients with invasive breast cancer who are recurrence-free for 5 years are classified as low risk for distant recurrence, patients may be able to safely forgo extended endocrine therapy.

Timing
The assays would be performed following the diagnoses of early-stage node-negative or node-positive invasive breast cancer, because patients are considering adjuvant chemotherapy.

The assays would be performed following the diagnosis of DCIS, because patients are considering RT.

The assays would be performed after 5 years of no recurrence of early-stage node-negative invasive breast cancer because patients are considering extended endocrine therapy.

Setting
The setting is a laboratory meeting general regulatory standards of the Clinical Laboratory Improvement Amendments.

Early-Stage Node-Negative Invasive Breast Cancer Considering Adjuvant Chemotherapy
Oncotype DX (21-Gene Assay)
Clinical Validity
We identified 4 studies meeting selection criteria (see Appendix 1).25-28 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 to develop the Oncotype algorithm, so its results might be biased.27 The study by Tang et al (2011)28 represents the same results as Paik et al (2004),26 but categorized by the Adjuvant! Online clinical risk stratifier (see Table 5).

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 the 10% threshold suggested by Henderson (2015),23 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 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 render different recurrence rates.

A prospective trial of Oncotype DX evaluating prognosis was published by Sparano et al (2015).29 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 (it should be noted 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.

Clinical Utility
No decision-impact studies were identified that provide clinical outcomes such as survival or recurrence. However, evidence for clinical validity has shown that Oncotype DX is able to identify women who can safely forgo adjuvant chemotherapy with tight precision, and thereby avoid negative effects of the therapy.

Section Summary: Oncotype DX (21-Gene Assay)
Multiple studies derived from archived samples of previously conducted randomized controlled trials (RCTs) have shown that a low RS is associated with a low absolute risk of 10-year distant recurrence with an upper 95% CI 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 5. 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></td>
<td>Low</td>
<td>Int</td>
</tr>
<tr>
<td>Paik et al (2004)</td>
<td>668</td>
<td>51</td>
<td>22</td>
</tr>
<tr>
<td>(TAM arm of NSABP B-14 trial)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paik et al (2006)</td>
<td>227</td>
<td>59</td>
<td>20</td>
</tr>
<tr>
<td>(TAM arm of NSABP B-20 trial)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buus et al (2016)</td>
<td>680</td>
<td>64</td>
<td>27</td>
</tr>
<tr>
<td>(ATAC trial)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tang et al (2011)</td>
<td>668</td>
<td>C lin low/RS low: 32</td>
<td>C lin low/RS int-high: 21</td>
</tr>
<tr>
<td>(TAM arm of NSABP B-14 trial)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ATAC: Arimidex, Tamoxifen, Alone or in Combination; Clin: Clinical; Int: Intermediate; NSABP: National Surgical Adjuvant Breast and Bowel Project; RS: Recurrence Score; TAM: tamoxifen.

EndoPredict
Clinical Validity
We identified 2 studies with 3 sets of findings that met selection criteria (see Table 6). The study by Filipits et al (2011) assessed patients from two previously conducted clinical trials.30 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 vs tamoxifen in postmenopausal women with localized breast cancer.25 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 expression profile (EP) score based solely on the gene expression assay; the EPclin score incorporates the EP score plus clinical data on tumor size and nodal status. Results of the subgroup of node-negative patients in both studies were only reported in supplementary materials because the main report focused on combined node-positive and node-negative results. Node-negative patients constituted 73% of the subjects included in Buus et al and 68% in Filipits 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 rates in the EP low-risk group. This demonstrated that EPclin discriminates outcomes better than EP; it also suggests that using EPclin would result in fewer patients choosing chemotherapy than using EP alone. Subgroup analyses in Filipits et al including only patients with node-negative cancers showed an absence of distant recurrence of 95.0% (95% CI, 93.2% to 97.6%) in the EPclin low-risk group and 83.6% (95% CI, 77.2% to 90.0%) in the EPclin high-risk group. Subgroup analyses in Buus et al reported distant recurrence-free rates of 94.1% in the EPclin low-risk group and 80.0% in the EPclin high-risk group.

Clinical Utility
No decision-impact studies were identified that provide clinical outcomes such as survival or recurrence. However, evidence for clinical validity has shown that EndoPredict is able to identify women who can safely forgo adjuvant chemotherapy with tight precision, and thereby avoid negative effects of the therapy.

Section Summary: EndoPredict
Three sets of findings, derived from archived samples of previously conducted RCTs, have shown that a low EP or low EPclin score is associated with a low absolute risk of 10-year distant recurrence with an upper 95% CI bound generally below 10%, except in a 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>
<thead>
<tr>
<th>Study (Source of Patients)</th>
<th>N</th>
<th>EP Low</th>
<th>EP High</th>
<th>EPclin Low</th>
<th>EPclin High</th>
<th>10-Year Distant Recurrence (95% Confidence Interval), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filipits et al (2011)³⁰,a (ABCSG-6 trial)</td>
<td>378</td>
<td>51</td>
<td>49</td>
<td>55</td>
<td>45</td>
<td>8 (3 to 13) / 22 (15 to 29) / 4 (1 to 8) / 28 (20 to 36)</td>
</tr>
<tr>
<td>Filipits et al (2011)³⁰,a (ABCSG-8 trial)</td>
<td>1324</td>
<td>48</td>
<td>52</td>
<td>65</td>
<td>35</td>
<td>6 (2 to 9) / 15 (11 to 20) / 4 (2 to 5) / 22 (15 to 29)</td>
</tr>
<tr>
<td>Buus et al (2016)²⁵ (ATAC trial)</td>
<td>680</td>
<td>43</td>
<td>57</td>
<td>73</td>
<td>27</td>
<td>3.0 (2 to 6) / 14.6 (11 to 19) / 5.9 (4 to 9) / 20.0 (15 to 27)</td>
</tr>
</tbody>
</table>


Breast Cancer Index
Clinical Validity
We identified 2 studies with 3 sets of findings of the BCI that met selection criteria (see Table 7).³¹,³² Some HER2-positive patients were included in both studies, but the number was not provided. Sgroi et al (2013) analyzed patients receiving anastrozole or tamoxifen in the ATAC trial.³³ This trial constitutes a Simon category B study. Two versions of the BCI score were generated in the study: (1) the BCI-C, based on cubic combinations of the variables, and (2) the
BCI-L, based on linear combinations of the variables. The second study, by Zhang et al (2013), reported 2 sets of findings, one 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, the BC1 classified more than half of the patients as low risk, and these patients had low risk of disease recurrence at 10 years. Sgroi et al report that the patients categorized as low risk by BCI-C and BCI-L experienced a low risk of disease recurrence, with the CIs not exceeding 10%. In the Zhang et al study, patients in BCI low-risk categories also showed a low risk of distant disease recurrence, with CIs not exceeding 10%.

Clinical Utility
No decision-impact studies were identified that report clinical outcomes such as survival or recurrence. However, evidence for clinical validity has shown that the BC1 is able to identify women who can safely forgo adjuvant chemotherapy with tight precision, and thereby avoid negative effects of the therapy.

Section Summary: Breast Cancer Index
Three sets of findings for the BC1 have shown a low risk of 10-year distant recurrence among patients classified at low risk. Two sets of findings have been derived from clinical trials and are categorized as Simon category B. The findings from the multicenter registry are Simon category C.

<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>BCI Low</td>
<td>BCI Int</td>
<td>BCI High</td>
<td>BCI Low</td>
</tr>
<tr>
<td>Zhang et al (2013)³² (multicenter registry)</td>
<td>358</td>
<td>55</td>
<td>22</td>
</tr>
<tr>
<td>Zhang et al (2013)³² (Stockholm trial)</td>
<td>317</td>
<td>64</td>
<td>20</td>
</tr>
<tr>
<td>BCI-C Low</td>
<td>BCI-C Int</td>
<td>BCI-C High</td>
<td>BCI-C Low</td>
</tr>
<tr>
<td>Sgroi et al (2013)³¹ (ATAC trial)</td>
<td>665</td>
<td>58</td>
<td>25</td>
</tr>
<tr>
<td>BCI-L Low</td>
<td>BCI-L Int</td>
<td>BCI-L High</td>
<td>BCI-L Low</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>25</td>
<td>16</td>
</tr>
</tbody>
</table>

ATAC: Arimidex, Tamoxifen, Alone or in Combination; BCI-C: Breast Cancer Index using cubic form of variables; BCI-L: Breast Cancer Index using linear form of variables.

MammaPrint (70-Gene Signature)
Clinical Validity
We identified 2 studies using MammaPrint that met selection criteria (see Table 8). Several studies could not be included due to mixed populations, including node-positive patients, mixed node-negative, and node-negative patients, or patients receiving chemotherapy.

The study by Bueno-de-Mesquita et al (2011) evaluated a mixed node-positive and node-negative population, but subgroup results were also calculated. The study sample was derived from 3 separate cohorts in cancer registry studies (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 are presented.
Only patients with both clinical low-risk scores and a MammaPrint low-risk score had 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.

In the van ’t Veer et al (2017) study, analyses were conducted on the Stockholm tamoxifen (STO-3) trial, which randomized patients with node-negative breast cancer to 2 years of tamoxifen, followed by an optional randomization for an additional 3 years to tamoxifen or no treatment. Both 10-year distant metastases-free survival (DMFS) and 20-year breast cancer–specific survival (BCSS) rates were calculated, by low-risk and high-risk groups, and by treatment group (tamoxifen vs no treatment). Patients receiving tamoxifen experienced longer DMFS and BCSS in both the low- and high-risk groups compared with patients not receiving tamoxifen.

Table 8. Ten- and 20-Year Follow-up Results by MammaPrint Risk Group

<table>
<thead>
<tr>
<th>Study (Source of Patients)</th>
<th>N</th>
<th>MP Risk Score Group, n (%)</th>
<th>10-Year DMFS, % (95% CI)</th>
<th>20-Year BCSS, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van ’t Veer et al (2017)</td>
<td>538</td>
<td>Low risk, with tamoxifen: 199 (37)</td>
<td>93 (88 to 96)</td>
<td>90 (84 to 94)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low risk, without tamoxifen: 172 (32)</td>
<td>83 (76 to 88)</td>
<td>80 (72 to 86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High risk, with tamoxifen: 82 (15)</td>
<td>85 (75 to 91)</td>
<td>83 (72 to 90)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High risk, without tamoxifen: 85 (16)</td>
<td>70 (58 to 79)</td>
<td>65 (53 to 75)</td>
</tr>
<tr>
<td>Bueno-de-Mesquita et al</td>
<td>139</td>
<td>Clin low/low MP low: 24</td>
<td>3 (0 to 9)</td>
<td></td>
</tr>
<tr>
<td>(2011) (3 combined cohorts)</td>
<td></td>
<td>Clin low/low MP high: 10</td>
<td>34 (9 to 59)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clin discordant MP low: 22</td>
<td>11 (0 to 22)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clin discordant MP high: 9</td>
<td>31 (6 to 56)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clin high/high MP low: 9</td>
<td>23 (0 to 46)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clin high/high MP high: 26</td>
<td>47 (31 to 63)</td>
<td></td>
</tr>
</tbody>
</table>

BCSS: breast cancer–specific survival; CI: confidence interval; Clin: clinical; DMFS: distant metastases-free survival; MP: MammaPrint.

*Confidence intervals provided by the manufacturer in October 2017.

Clinical Utility

The MINDACT trial (Cardoso et al, 2016) is a prospectively designed trial evaluating MammaPrint, with additional randomized components. Currently, 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 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. Investigators prespecified that the upper bound of the 95% CI 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 scores. 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 with the other studies discussed herein, BCBSA staff abstracted the results of these supplemental analyses (see Table 9). 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 had a distant recurrence rate of 4.5% (95% CI, 3.8% to 8.4%).

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 less informative regarding whether chemotherapy is or is not beneficial in these patient groups. In the main study, the hazard ratio (HR) for chemotherapy in the high clinical risk/low genomic risk was 0.78 (95% CI, 0.5 to 1.21). The HR for chemotherapy in the low clinical risk/high genomic risk group was 1.17 (95% CI, 0.59 to 2.28).

Table 9. 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)</td>
<td>4225</td>
<td>Clin low/MP low: 58</td>
<td>2.4 (1.8 to 3.1)</td>
</tr>
<tr>
<td>(MINDACT trial)</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&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.1 (6.8 to 12)</td>
</tr>
</tbody>
</table>

Clin: clinical; HER2: human epidermal growth factor receptor 2; MINDACT: Microarray In Node-negative and 1 to 3 positive lymph node Disease may Avoid Chemotherapy; MP: MammaPrint.
<sup>a</sup> All clin high/MP high subjects received chemotherapy.

Section Summary: MammaPrint (70-Gene Signature)

One Simon category C study and 1 Simon category B study have been evaluated MammaPrint and provided 10-year distant recurrence outcomes. In the category C 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 was small, and the proportion of patients identified at low risk was a small proportion (24%) of the study sample. The category B study showed that receiving tamoxifen improved recurrence and survival, in both low- and high-risk groups. The Simon category A study of MammaPrint has currently provided only 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

Clinical Validity

Two studies that met selection criteria were identified (both studies are classed as Simon category B).36,37 However, the distant recurrence rates from the study by Dowsett et al (2013) were not directly reported in the published article. As a result, rates cited in Table 10 are based on visual estimates of the graphic results; CIs are not available.36 Both studies reported distant recurrence rates below 5% with the CIs 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.

Clinical Utility

No decision-impact studies were identified that report clinical outcomes such as survival or recurrence. However, evidence for clinical validity has shown that the assay is able to identify women who can safely forgo adjuvant chemotherapy with tight precision, and thereby avoid negative effects of the therapy.

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 10. 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 Distance 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) (ABC SG-8 trial)37</td>
<td>1047</td>
<td>47</td>
<td>32</td>
</tr>
<tr>
<td>Dowsett et al (2013)36 (ATAC trial)</td>
<td>739</td>
<td>59</td>
<td>33</td>
</tr>
</tbody>
</table>

ABC SG: Austrian Breast and Colorectal Cancer Study Group; ATAC: Arimidex, Tamoxifen, Alone or in Combination; Int: intermediate; NR: not reported.

Early-Stage Node-Positive Invasive Breast Cancer Considering Adjuvant Chemotherapy

Five studies that met selection criteria were identified (see Appendix 1), all prospective-retrospective designs, examining the prognostic value of gene expression profiling tests in patients with early-stage node-positive breast cancer receiving only endocrine therapy. Oncotype DX RS was evaluated in 2 studies,38,39 Prosigna ROR (risk of recurrence)40 in 1 study, and EndoPredict in 2 studies. Albain et al (2010) also explored a possible role for Oncotype DX in predicting chemotherapy benefit.38 We also discuss results from the MINDACT trial, a prospectively designed trial evaluating MammaPrint. Table 11 displays the characteristics of patients assessed across the prospective-retrospective analyses. Almost all cancers were estrogen receptor-positive and HER2-negative, most patients had three or fewer positive lymph nodes, and all women were postmenopausal.

Table 11. Characteristics of Patients Included in Node-Positive Prospective-Retrospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Tumor Size, n (%)</th>
<th>Nodes, n (%)</th>
<th>Adjuvant Chemo n (%)</th>
<th>Trial/Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncotype DX</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albain (2010)38a</td>
<td>148</td>
<td>145 (98)</td>
<td>13 (9)</td>
<td>64 (31)</td>
</tr>
<tr>
<td>Albain (2010)38b</td>
<td>219</td>
<td>210 (96)</td>
<td>30 (14)</td>
<td>74 (34)</td>
</tr>
</tbody>
</table>
Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer

Table 12 displays 10-year event rates reported by risk categories. Distant recurrence rates were not reported by Albain et al, but the 60% ten-year disease-free survival in the low-risk group would suggest substantial event rates in patients not receiving adjuvant chemotherapy. Confidence intervals were not reported, but given the small number of low-risk patient intervals, would likely include a large range of plausible estimates. Dowsett et al (2010) reported a 17% distant recurrence rate (death was considered a censoring event) in the low-risk category. Finally, Gnant et al (2015) reported 10-year distant recurrence rates in the Prosigna low-risk group with a single positive node of 6.6% (as much as 2-fold greater than for Prosigna-classified low-risk node-negative patients; see Table 11) with an upper bound of the 95% CI of 12.8%. None of the studies reported the ability of tests to reclassify after assigning risk based on clinical predictors.

Table 12. 10-Year Event Rates According to Risk Categories in Identified Prospective-Retrospective Studies

<table>
<thead>
<tr>
<th>Test</th>
<th>Sample</th>
<th>Low Outcome</th>
<th>95% CI</th>
<th>Risk Category</th>
<th>Intermediate Outcome</th>
<th>95% CI</th>
<th>High Outcome</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncotype DX</td>
<td>Albain, Tamoxifen</td>
<td>148</td>
<td>60%</td>
<td>77% (49-97)</td>
<td>48</td>
<td>48%</td>
<td>68% (38-91)</td>
<td>47</td>
</tr>
<tr>
<td>Dowsett 2010 (5-year outcomes)</td>
<td>296</td>
<td>17%</td>
<td>(12-24)</td>
<td>94</td>
<td>28%</td>
<td>(20-49)</td>
<td>52</td>
<td>49%</td>
</tr>
<tr>
<td>EndoPredict</td>
<td>Filipps (2011)</td>
<td>537</td>
<td>15%</td>
<td>NR</td>
<td>240</td>
<td>15%</td>
<td>NR</td>
<td>267</td>
</tr>
<tr>
<td>Buus 2016 (EP score)</td>
<td>248</td>
<td>23.1%</td>
<td>(13.9-31.9)</td>
<td>194</td>
<td>26%</td>
<td>(15.9-43.1)</td>
<td>164</td>
<td>36%</td>
</tr>
<tr>
<td>Prosinga</td>
<td>Gnant 2015, 1 N+</td>
<td>351</td>
<td>6.6%</td>
<td>(3.3-12.8)</td>
<td>106</td>
<td>15.5%</td>
<td>(9.5-25.6)</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>Gnant 2015, 2-3 N+</td>
<td>212</td>
<td>12.5%</td>
<td>(6.8-22.8)</td>
<td>83</td>
<td>12.5%</td>
<td>(6.8-22.8)</td>
<td>129</td>
</tr>
</tbody>
</table>

CI: confidence interval; DFS: disease-free survival; DR: distant recurrence; NR: not reported; OS: overall survival.

a Death from any cause considered a censoring event.
b Death from breast cancer included as a distant recurrence.
c Combined low- and intermediate-risk categories.

Oncotype DX (21-Gene Assay)

Clinical Validity

Albain et al (2010) analyzed data from the Southwest Oncology Group Trial 8814, an RCT that enrolled estrogen receptor-positive postmenopausal women and compared cyclophosphamide, doxorubicin, and fluorouracil chemotherapy followed by tamoxifen (CAF-T) for 5 years with tamoxifen alone. Archived samples from 41% (n=148) and 39% (n=219) of the 2
trial arms, respectively, were available for analysis, and patients included in the analyses had fewer positive nodes and smaller tumors than those in the overall trial. Based on the RS results (includes HER2 assay), about 1 in 10 patients had a HER2-positive tumor. The primary end point was disease-free survival (time from enrollment to locoregional or distant recurrence, new primary cancer, or any cause of death). Neither distant disease-free survival nor distant recurrence rates were available for analysis.

In addition to examining the prognostic value of the RS in node-positive patients, its potential predictive ability was also analyzed (see Table 13). While the hazard ratios appeared to vary with time, the magnitude differed by RS category, raising the possibility that adjuvant chemotherapy might not benefit those with low-risk scores. However, the CIs for the low-risk group include HRs consistent with benefit, and the small number of patients studied precludes drawing conclusions.

Table 13. Hazard Ratios for Chemotherapy Benefit of Sequential CAF-T vs Tamoxifen Alone by Oncotype DX RS

<table>
<thead>
<tr>
<th>Variables</th>
<th>OS, HR (95% CI)</th>
<th>DFS, HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 Years</td>
<td>≤5 Years</td>
</tr>
<tr>
<td>Parent trial</td>
<td>0.78 (0.63 to 0.97)</td>
<td>0.68 (0.53 to 0.84)</td>
</tr>
<tr>
<td>RS sample</td>
<td>0.77 (0.52 to 1.14)</td>
<td>0.79 (0.53 to 0.86)</td>
</tr>
<tr>
<td>Low RS</td>
<td>1.34 (0.47 to 3.82)</td>
<td>0.88 (0.38 to 1.92)</td>
</tr>
<tr>
<td>Intermediate RS</td>
<td>0.95 (0.43 to 2.14)</td>
<td>0.52 (0.20 to 1.52)</td>
</tr>
<tr>
<td>High RS</td>
<td>0.59 (0.32 to 1.11)</td>
<td>0.60 (0.22 to 1.62)</td>
</tr>
</tbody>
</table>

Adapted from Albain et al (2010).38
CAF-T: cyclophosphamide, doxorubicin, and fluorouracil chemotherapy followed by tamoxifen; CI: confidence interval; DFS: disease-free survival; HR: hazard ratio; RS: Recurrence Score; OS: overall survival.

Oncotype DX risk score appears to be associated with 10-year distant recurrence-free survival in patients with node-positive disease, although, as expected, the recurrence rates for the node-positive disease are higher than for node-negative (i.e., 10-year distant recurrence-free survival in Albain et al). Overall, there is significant uncertainty in the estimates, and only 1 Simon category B study has reported on point-estimates for 10-year distant recurrence-free survival with CIs.

Dowsett et al (2010) examined a sample of node-negative and node-positive patients from the ATAC trial (Simon category B).39 Archived samples were available for 306 node-positive patients of whom 243 (80%) had 1 to 3 involved nodes. The 9-year distant recurrence rate (censoring for any cause of death) in low-risk node-positive patients was 17% (95% CI, 12% to 24%) compared with 4% (95% CI, 3% to 7%) for the low-risk node-negative group. OS rates by risk group were similar to those reported by Albain et al. Dowsett et al fitted a model to recurrence rates using a continuous risk score and number of nodes, which suggested considerably lower recurrence rates with 1 to 3 nodes compared with 4 or more. A potential predictive effect was not examined and OS not reported.

Although the RS appears to have some prognostic ability across the risk categories for node-positive disease, the absolute distant recurrence rates in the low-risk group were considerably higher than those proposed to be low enough to lead patients to forgo adjuvant chemotherapy in low-risk node-negative patients. There is a wide range of survival improvements over which individual patients would elect or refuse adjuvant chemotherapy, but accurate risk estimates are needed so that patients can make informed decisions. Given that patients would typically elect adjuvant chemotherapy for a modest improvement in survival (almost 50% reported that
they would choose it for even a 1% gain)20,23 raises a question whether in practice the RS offers sufficient prognostic information to inform decisions.

Nitz et al (2017) conducted a phase 3 Plan B trial with a mixed population of women with node-negative and node-positive breast cancer.41 The trial was initially designed to compare anthracycline-containing chemotherapy with anthracycline-free therapy. An amendment was made to recommend endocrine therapy alone for patients with pN0/pN1 breast cancer and an RS of 11 or less. A total of 2642 patients were included in the trial. Median age was 56 years, 59% were node-negative, 35% were pN1, and 6% were pN2-3. Details of subgroup analyses of node-positive patients were limited. The authors stated that 5-year OS in patients with an RS between 12 and 25 was significantly higher than in patients with an RS greater than 25 within all nodal subgroups and that 5-year OS in low RS patients was higher compared with high RS patients in all nodal subgroups, but rates and CIs were not provided.

**Clinical Utility**

No decision-impact studies were identified that report clinical outcomes such as survival or recurrence. Studies providing evidence for the clinical validity of Oncotype DX for patients with node-positive breast cancer have reported imprecise estimates of survival improvements in patients classified as low risk.

**Section Summary: Oncotype DX (21-Gene Assay)**

Results from prospective-retrospective Simon category B studies have suggested uncertainty in the estimates of the distant recurrence-free survival risk for patients in different Oncotype DX RS categories. One study did not report CIs for the estimates of survival and, in the other, the CIs were very wide. Another study mentioned that OS was significantly higher in patients with a low RS, but rates were not provided. Although it is expected that the distant recurrence-free survival estimates will be lower than those experienced by patients with node-negative disease, more certain estimates of risk are needed before a reasonable discussion about whether patients would or should decline adjuvant chemotherapy can occur. Albain et al (2010) suggested the test might also be predictive, albeit based on a small sample. Although there has been substantial adoption of the RS to inform adjuvant chemotherapy choices in node-positive patients, convincing evidence that decisions based on test results will improve outcomes is lacking, and guidelines do not offer support.44 The ongoing RxPONDER trial is randomizing patients with early-stage estrogen receptor-positive, HER2-negative breast cancer and 1 to 3 positive nodes, stratified by RS (0 to 13, 14 to 25) to adjuvant chemotherapy or no adjuvant chemotherapy. Results of that trial will most likely define the clinical utility of the RS in node-positive patients.

**EndoPredict**

**Clinical Validity**

Filipits et al (2011) evaluated the potential prognostic value of the EndoPredict EP and EPclin risk scores among node-positive patients in a combined analysis of ABCSG-6 and ABCSG-6 trial samples (Simon category B).30 Of the 537 node-positive patients, 85% had a single positive node, 240 were classified as EP low risk, and 297 were classified as EP high risk. The 10-year absence of distant recurrence for node-positive patients was shown in a Kaplan-Meier curve in the article supplement. The 10-year absence of distant recurrence estimate for node-positive patients appears to be about 85% in EP low-risk and 73% in EP high-risk patients based on visual inspection; CIs were not provided. The 10-year absence of distant recurrence estimates for the EPclin low-risk group and EPclin high-risk group were 94.9% (95% CI, 90.8% to 99.0%) and 72.2% (95% CI, 65.6% to 78.8%), respectively.

Buus et al (2016) also reported on the prognostic value of EndoPredict among node-positive patients from ATAC in the article supplement (Simon category B).25 Of the 248 node-positive patients, 80% had a single positive node, 94 were classified as EP low risk, and 154 were classified as EP high risk; 47 were classified as EPclin low risk, and 201 were classified as EPclin high risk. The
10-year distant recurrence-free survival for EP low and high risk were 21.3% (95% CI, 13.9% to 31.9%) and 36.4% (95% CI, 28.9% to 45.2%), respectively. The 10-year distant recurrence-free rate for EPclin low and high risk were 5.0% (95% CI, 1.2% to 18.9%) and 36.9% (95% CI, 30.2% to 44.5%), respectively.

**Clinical Utility**
No decision-impact studies were identified that report clinical outcomes such as survival or recurrence. One of the 2 Simon category B studies provided evidence for clinical validity with tight precision, which would allow for the identification of women who can safely forgo adjuvant chemotherapy. The second study also reported a low point estimate; however, the wide CIs exceeded 10%.

**Section Summary: EndoPredict**
Two Simon category B studies, which met inclusion criteria, were identified. For node-positive, EPclin low-risk patients, the 10-year distant recurrence rate estimates was 5% (it should be noted that 1 study had a precise estimate while the other study had wide CIs, and the upper bound for the 95% CI was well above the range judged clinically informative in node-negative patients).

**Breast Cancer Index**
No studies were identified that met inclusion criteria in node-positive study populations for the BCI test.

**70-Gene Signature (MammaPrint)**

**Clinical Utility**
The previously described MINDACT study (Simon category A) initially enrolled only patients with node-negative disease but began including women with 1 to 3 positive nodes in 2009. Subgroup results were reported from the randomized MINDACT comparison of adjuvant chemotherapy with no chemotherapy in node-positive patients who were classified as high-risk based on clinical criteria and low-risk based on genetic risk with MammaPrint.35 Overall, the study included 1404 node-positive patients; 296 (16%) with 1 positive node, 114 (6%) with 2 positive nodes, 65 (4%) with 3 positive nodes, and 2 (0.1%) with 4 or more positive nodes. In the high clinical risk and low genetic risk group, 353 node-positive patients were randomized to chemotherapy, and 356 node-positive patients were randomized to no chemotherapy. The 5-year distant recurrence was 3.7% (95% CI, 1.9% to 6.9%) in the chemotherapy group and 4.4% (95% CI, 2.6% to 7.3%) in the no chemotherapy group (HR=0.88; 95% CI, 0.42 to 1.82; p=0.72). MINDACT has currently only provided 5-year distant recurrence outcomes; high clinical risk, low genetic risk patients may not be at low enough risk to defer chemotherapy because these 5-year recurrence rates will probably be higher at 10 years.

Mook et al (2009) evaluated the prognostic value of MammaPrint in patients with node-positive breast cancer.45 Patients were selected from consecutive series of breast cancer patients from 2 institutions (Simon category C). A total of 241 patients were included, 99 were classified as low risk, and 142 were classified as high risk. Fifty-one percent of the patients had 1 positive node, 32% had 2 positive nodes, and 17% had 3 positive nodes. Median follow-up was 7.8 years. Ten-year BCSS was 96% (standard error [SE], 2%) for the low-risk group and 76% (SE=4%) for the high-risk group. The probability of remaining distant metastases-free at 10 years was 91% (SE=4%) for the low-risk group and 76% (SE=4%) for the high-risk group.

**Section Summary: MammaPrint**
One Simon category A study and 1 Simon category C study have investigated the use of MammaPrint to assess distant recurrence risk in women with node-positive breast cancer. The category C study reported 10-year follow-up results, which showed that patients categorized as low risk experienced better survival and recurrence rates than patients categorized as high risk. However, the recurrence rate with standard error did not meet the threshold benefit of less than 10%. The Simon category A study found 5-year distant recurrence rates for treated and
untreated women are similar, which would indicate that the low-risk patients can safely forgo adjuvant chemotherapy. Longer follow-up is necessary for confirmation of the category A study results.

**Prosigna Clinical Validity**

Gnant et al (2015) examined the potential prognostic value of the PAM50 ROR score, including clinical predictors, among node-positive patients in a combined analysis of the ABCSG-8 and ATAC trial samples. Samples from 543 patients treated with endocrine therapy alone were included, and 10-year distant recurrence (the primary end point) analyzed. Among patients with a single positive node and a low-risk score, a 10-year distant recurrence occurred in 6.6% (95% CI, 3.3% to 12.8%). In all other risk categories or with 2 to 3 positive nodes, distant recurrence rates were considerably higher with upper bounds for the 95% CIs of 25% or more. OS was not included in the report.

**Clinical Utility**

No decision-impact studies were identified that provide clinical outcomes such as survival or recurrence. One study provided evidence for clinical validity. The point estimate for the 10-year distant recurrence rate was 7% however, the CI was large and did not meet the threshold benefit of less than 10%.

**Section Summary: Prosigna**

One Simon category B study meeting inclusion criteria was identified. The 10-year distant recurrence rate in patients with a single positive node and low-risk ROR scores is about 2-fold the rate in node-negative patients with low-risk ROR scores. The 10-year distant recurrence rate estimate for node-positive, low-risk patients had an upper bound for the 95% CI approaching the range judged clinically informative in node-negative patients. Additional studies are needed to confirm the magnitude and precision of the estimates.

**Ductal Carcinoma In Situ Considering Radiotherapy**

**Oncotype DX Breast Ductal Carcinoma In Situ Score**

**Clinical Validity**

DCIS 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; 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 radiotherapy. Thus, accurate prediction of recurrence risk may identify those women who can 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 ES194 study, Solin et al (2013) compared the 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). This study is Simon category B. The continuous Oncotype DX Breast DCIS Score was significantly associated with developing either a local recurrence or invasive carcinoma (HR=2.31; 95% CI, 1.15 to 4.49; p=0.02) whether or not patients were treated with tamoxifen. The prespecified DCIS risk groups of low, intermediate, and high had 10-year risks
of developing either a local recurrence or invasive carcinoma of 11%, 27%, and 26%, respectively. This study addressed the development of the Oncotype DX Breast DCIS Score and clinical validity (association of the test result 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. This study is Simon category C. Median follow-up for the 571 women was 9.6 years. There were 100 local recurrence events—43 were DCIS, and 57 were invasive cancer. The 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.

Clinical Utility
No decision-impact studies were identified that provide clinical outcomes such as survival or recurrence. Two studies provided evidence for the clinical validity of the Oncotype DX DCIS score; however, the recurrence risk estimates for the low-risk group were not low enough or precise enough (did not meet the threshold of 10%).

Section Summary: Oncotype DX Breast Ductal Carcinoma In Situ Score
Evidence consists of 1 Simon category B study and 1 Simon category C study. Based on the Oncotype DX Breast DCIS Score of low risk for recurrence, it is unclear whether estimated recurrence risks for this group are low enough or estimated with sufficient precision (point-estimates and CIs included the threshold of 10%) to meaningfully affect the decision to have or to forgo radiotherapy.

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

Extended Adjuvant Endocrine Therapy Beyond 5 Years
Multiple randomized controlled trials have demonstrated improvements in overall and BCSS outcomes with 5 to 10 years of tamoxifen for estrogen receptor-positive tumors. However, extended adjuvant endocrine therapy may be associated with serious adverse events, including pulmonary embolism, endometrial cancer, osteoporosis, and fractures. Common side effects—hot flashes, sexual dysfunction, and musculoskeletal symptoms—often lead to poor compliance, with as many as 40% of patients discontinuing treatment after 3 years. Accurately identifying low-risk patients who might obtain little benefit from extended endocrine therapy could allow patients to make treatment decisions consistent with how they value the potential benefits and harms.

In the absence of direct evidence that gene expression profiling tests improve outcomes in women considering extended endocrine therapy, the following need to be considered: (1) the expected magnitude and certainty of benefit from extended endocrine therapy, (2) how women value harms relative to benefit, and the range of thresholds in risk that a test is likely to change decisions, (3) whether a test accurately discriminates good from poor outcomes (i.e., prognostic value for recurrences) at those thresholds, and (4) whether the test provides incremental improvement over clinical risk prediction algorithms or tools.
Seven studies (see Table 14) meeting selection criteria (see Appendix 1) were identified that examined the prognostic value of a gene expression profiling test for late recurrences after 5 years of endocrine therapy. All 7 studies were prospective-retrospective designs of patients with early-stage node-negative or node-positive breast cancer receiving up to 5 years of endocrine therapy. One study (2013) examining prognosis and an additional nested case-control study (Sgroi et al, 2013) analyzed the potential predictive value of the HOXB13/IL17BR (H/I) index included in the BCI test. All but 1 cohort analyzed in Zhang et al (2013) included only postmenopausal women. In addition, samples overlapped across some studies, as shown in the table by the trials used for analysis. Tables 15-19 display results from studies of prognosis subsequently discussed.

**Table 14. Characteristics of Patients in Extended Endocrine Therapy Studies of Prognosis or Predicting Treatment Benefit**

<table>
<thead>
<tr>
<th>Study</th>
<th>Tumor Size, n (%)</th>
<th>Nodes, n (%)</th>
<th>Adjuvant Chemo, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>≤2 cm</td>
<td>&gt;2 cm</td>
</tr>
<tr>
<td><strong>Oncotype DX</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sestak (2013)</td>
<td>940</td>
<td>683 (73)</td>
<td>257 (27)</td>
</tr>
<tr>
<td><strong>EndoPredict</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dubsky (2013)</td>
<td>1702</td>
<td>1136 (67)</td>
<td>563 (33)</td>
</tr>
<tr>
<td><strong>Breast Cancer Index</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhang (2013)</td>
<td>285</td>
<td>259 (82)</td>
<td>55 (17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>358</td>
<td>237 (66)</td>
</tr>
<tr>
<td>Sgroi (2013)</td>
<td>597</td>
<td>442 (74)</td>
<td>155 (26)</td>
</tr>
<tr>
<td>Sgroi (2013)</td>
<td>249</td>
<td>110 (44)</td>
<td>139 (56)</td>
</tr>
<tr>
<td><strong>MammaPrint</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esserman (2017)</td>
<td>652</td>
<td>499 (77)</td>
<td>145 (22)</td>
</tr>
<tr>
<td><strong>Prosigna</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filipits (2014)</td>
<td>1246</td>
<td>NR (see below)</td>
<td>919 (74)</td>
</tr>
<tr>
<td>Sestak (2013)</td>
<td>940</td>
<td>683 (73)</td>
<td>257 (27)</td>
</tr>
<tr>
<td>Sestak (2015)</td>
<td>862</td>
<td>587 (68)</td>
<td>275 (32)</td>
</tr>
<tr>
<td>Sestak (2015)</td>
<td>1275</td>
<td>938 (74)</td>
<td>337 (26)</td>
</tr>
</tbody>
</table>

ABC SG: Austrian Breast and Colorectal Cancer Study Group; Chemo: chemotherapy; NR: not reported; TAM: tamoxifen; TransATAC: translational substudy of the Arimidex, Tamoxifen, Alone or in Combination. Sample size and characteristics represent patients at enrollment for Dubsky et al (2013).
Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer

Table 15. Prognosis for Late Distant Recurrence Based on Gene Expression Profiling Test Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Study</th>
<th>N</th>
<th>Years</th>
<th>Low Risk Category</th>
<th>Intermediate Risk Category</th>
<th>High Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCI</td>
<td>Zhang 2013 (Stockholm TAM)</td>
<td>356</td>
<td>5-10</td>
<td>n: 148</td>
<td>n: 155</td>
<td>n: 43</td>
</tr>
<tr>
<td></td>
<td>Zhang 2013 (Cohort study)</td>
<td>312</td>
<td>5-10</td>
<td>n: 105</td>
<td>n: 155</td>
<td>n: 61</td>
</tr>
<tr>
<td>Sigo 2013</td>
<td>356</td>
<td>5-10</td>
<td>366</td>
<td>n: 148</td>
<td>n: 166</td>
<td>n: 44</td>
</tr>
<tr>
<td>Proligna</td>
<td>Talcott 2014</td>
<td>312</td>
<td>5-10</td>
<td>n: 105</td>
<td>n: 155</td>
<td>n: 61</td>
</tr>
<tr>
<td></td>
<td>Sestak 2015</td>
<td>900</td>
<td>5-10</td>
<td>n: 148</td>
<td>n: 166</td>
<td>n: 44</td>
</tr>
<tr>
<td></td>
<td>Sestak 2015, all patients</td>
<td>213</td>
<td>5-10</td>
<td>n: 105</td>
<td>n: 155</td>
<td>n: 61</td>
</tr>
<tr>
<td></td>
<td>Sestak 2015, node negative</td>
<td>356</td>
<td>5-10</td>
<td>n: 148</td>
<td>n: 166</td>
<td>n: 44</td>
</tr>
</tbody>
</table>


Note that, except for Filipits et al (2014), recurrences are over 5-year periods, or shorter than reported for adjuvant chemotherapy.


Oncotype DX (21-Gene Assay)

Clinical Validity

Sestak et al (2013) (previously discussed with the TransATAC study) also displayed late distant recurrences for risk categories of Oncotype DX in a Kaplan-Meier curve without confidence intervals. The cumulative distant recurrence rate in the low-risk group between 5 and 10 years was estimated at 7.6%, or considerably higher than for any of the other tests considered. That result was consistent with the higher annualized hazard found in those years compared with PAM50 ROR. These limited results do not suggest a role for Oncotype DX for predicting late recurrences.

Clinical Utility

No decision-impact studies were identified that report clinical outcomes such as survival or recurrence. No studies comparing genetic test classifications with clinical risk prediction tools were identified. One study provided evidence for clinical validity; the limited results did not support the clinical utility of Oncotype DX for this indication.

Section Summary: Oncotype DX

Evidence for the use of Oncotype DX for the prognosis of risk recurrence in women considering extending endocrine therapy beyond 5 years consists of a single study. The point estimate of risk was high, and CIs were not provided. Additional evidence would be needed to consider this indication.

EndoPredict

Clinical Validity

Dubsky et al (2013) analyzed late recurrences from patients in the ABCSG6 and ABCSG8 trials (see Table 14) treated with 5 years of endocrine therapy (tamoxifen for 5 years or tamoxifen for 2 years followed by anastrozole for 3 years). Although 32% of patients were node-positive, none received adjuvant chemotherapy. Of the 1702 enrolled patients with estrogen receptor-positive HER2-negative cancers, follow-up was analyzed for 998 patients free of recurrence over 5 years and untreated with extended endocrine therapy. Risk categories were assigned based on gene expression profile (EP) alone and combined with a score that included nodal status and tumor size (EPclin). In the EP low-risk group, between 5 and 10 years the cumulative late distant recurrence rate was 3.7% (95% CI, 0.9% to 6.5%) (see Table 15). The distant recurrence rate in the EP high-risk group was 9% (CIs not reported). Adding clinical predictors suggested fewer late distant recurrences in the low-risk group (see Table 15). The risk of late distant recurrence in the node-negative patients (from digitized supplemental figure) was 3.6% or comparable with the overall EP low-risk group (n=503).
EP and EPclin appear to be able to identify a group at low risk of distant recurrence from years 5 to 10 in this prospective-retrospective study (Simon category B) of patients untreated with adjuvant chemotherapy enrolled in the ABCSG-6 and -8 trials. In the current environment, a significant proportion of high-risk patients would have been treated with adjuvant chemotherapy based on a gene expression profiling result. C statistics (area under the receiver operating characteristic curve) were reported to support incremental improvement with the EP or EPclin over Adjuvant! Online or nodal status, tumor size, or grade. However, they appeared to include EP and EPclin as continuous variables and not threshold cutoffs for those tests that would inform decisions.

**Clinical Utility**

No decision-impact studies were identified that report clinical outcomes such as survival or recurrence. No studies comparing genetic test classifications with clinical risk prediction tools were identified. One study provided evidence for clinical validity, showing that EP and EPclin scores adequately predicted the risk of distant recurrence, which would allow for the identification of women who can safely forgo extended endocrine therapy.

**Section Summary: EndoPredict**

One Simon category B study with some limitations found EndoPredict (EP and EPclin) prognostic for late distant recurrences. At least 2 Simon category B studies showing results consistent with clinical utility are necessary to demonstrate adequate evidence. In addition, studies comparing genetic test classifications with clinical risk prediction tools are needed.

**Breast Cancer Index**

**Breast Cancer Index Prognosis**

The prognostic component of BCI is based on the combination of an endocrine response biomarker H/I and a proliferation biomarker (Molecular Grade Index). These indices are used to categorize patients into groups of high and low risk for distant recurrence.

**Clinical Validity**

Incorporating the BCI as a continuous variable, Zhang et al (2013) developed an "optimized model" to predict early and late distant recurrences.32 Patient samples from 2 studies were used (see Table 14): the Stockholm trial (Simon category B), which compared 2 or 5 years of tamoxifen with no treatment in early-stage breast cancer; and a cohort (Simon category C) of estrogen receptor-positive lymph node-negative patients retrospectively identified from a U.S. university medical center and a hospital (patients were treated between 1990 and 2000). Most patients were HER2-negative, with 5% of the Stockholm trial HER2-positive, and 10% of the cohort HER2-positive. Data from patients in the untreated arm of the Stockholm trial were used for model development; the tamoxifen arm of the trial and the 2-institution cohort were used for validation. The primary end point was distant recurrence-free survival (censoring for any cause of death). The Stockholm trial enrolled postmenopausal women who did not receive adjuvant chemotherapy; the 2-institution cohort included premenopausal and postmenopausal women of whom one-third received adjuvant chemotherapy (see Table 14). A median follow-up of 10 years was analyzed with distant recurrences occurring in 16% of all patients over 10 years. In the validation tamoxifen-treated arm of the Stockholm trial, there were 20 late distant recurrences and 65% of patients were classified as low risk; in the 2-institution cohort, there were 23 late distant recurrences, and 58% of patients were classified as low risk.

From years 5 to 10, distant recurrence rates were low in the low-risk groups of the validation samples (see Table 15). The results support the prognostic value of the BCI for late recurrences in node-negative patients. About one-third (32%) of the cohort received adjuvant chemotherapy, but whether any of those patients were at low BCI risk was not noted. However, the authors reported chemotherapy was not associated with a lower risk of late recurrence.
Sgroi et al (2013) examined late distant recurrences among 597 estrogen receptor-positive, HER2-negative, node-negative patients from the ATAC trial (Simon category B) not treated with adjuvant chemotherapy.31 Patients who died were censored in the analysis of distant recurrences. In the analytic sample, distant recurrences occurred among 4% of patients in years 0 to 5 and among 7% in years 5 to 10. From years 5 to 10, in the BCI low-, intermediate-, and high-risk groups’ distant recurrence rates were 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%), respectively. But when examined as a continuous predictor for late recurrence (using the model developed by Zhang et al32), at a value of 5 (which is categorized as low risk), the predicted distant recurrence rate was 6.8% (95% CI, 4.7% to 9.1%) (CIs were provided by the manufacturer in October 2017).

The authors concluded: “…our results suggest that BCI might have the potential to influence two important decisions in the management of postmenopausal patients with oestrogen-receptor-positive, N0 breast cancer; first at the time of diagnosis and second at 5-year disease-free follow-up.” These results would suggest that the BCI has prognostic value for late distant recurrences over a 5- to 10-year period. Among the higher risk patients, none received adjuvant chemotherapy or therapy not consistent with test results; the accuracy of late recurrence predictions in those patients is uncertain.

 Schroeder et al (2016)55 calculated distant recurrence-free survival (DRFS) rates following 5 years of endocrine therapy among the subset of patients with clinically low-risk (T1N0) breast cancer from the 2 populations studied by Zhang et al (2017). The Stockholm trial had 237 patients, and the U.S. medical center cohort contributed 210 patients that were T1N0. The BCI classified 68% (160/237) and 64% (135/210) of the Stockholm population and the medical center population as low risk, respectively. Median follow-up was 17 years for the Stockholm study and 10 years for the medical center cohort. Table 16 lists the 5- to 15-year distant recurrence-free survival rates (as categorized by BCI risk) for the 2 trial populations.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Low Risk, % (95% CI)</th>
<th>High Risk, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schroeder et al (2016)55</td>
<td>Stockholm T1N0 total</td>
<td>237</td>
<td>95.4 (92.1 to 98.8)</td>
<td>86.7 (78.9 to 95.3)</td>
</tr>
<tr>
<td></td>
<td>Stockholm T1N0 HER2-negative</td>
<td>225</td>
<td>95.2 (91.9 to 98.8)</td>
<td>86.9 (78.8 to 95.9)</td>
</tr>
<tr>
<td></td>
<td>Stockholm T1N0 HER2-negative, G1 &amp; G2</td>
<td>204</td>
<td>95.7 (92.5 to 99.1)</td>
<td>90.4 (82.8 to 98.8)</td>
</tr>
<tr>
<td></td>
<td>Multi-institutional T1N0 total</td>
<td>210</td>
<td>98.4 (96.3 to 100)</td>
<td>89.6 (82.4 to 97.4)</td>
</tr>
<tr>
<td></td>
<td>Multi-institutional T1N0 HER2-negative</td>
<td>190</td>
<td>98.4 (96.1 to 100)</td>
<td>87.5 (79.1 to 96.9)</td>
</tr>
<tr>
<td></td>
<td>Multi-institutional T1N0 HER2-negative, G1 &amp; G2</td>
<td>173</td>
<td>98.2 (95.8 to 100)</td>
<td>87.6 (78.5 to 97.7)</td>
</tr>
</tbody>
</table>

CI: confidence interval; DRFS: distant recurrence-free survival; HER2: human epidemal growth factor receptor 2.

Clinical Utility
No decision-impact studies were identified that report clinical outcomes such as survival or recurrence. Evidence for clinical validity has shown that the BCI is able to identify women who can safely forgo extended endocrine therapy with tight precision, and thereby avoid negative effects of the therapy. However, no studies comparing genetic test classifications with clinical risk prediction tools were identified.

Breast Cancer Index Prediction
The endocrine predictive component of the BCI is based on the H/I ratio alone, in which a high H/I ratio predicts the likelihood of benefit from extended endocrine therapy.
Clinical Validity

Sgroi et al (2013) conducted a prospective-retrospective, nested case-control study within the MA.17 trial that compared extended endocrine therapy (letrozole) with placebo in postmenopausal women with hormone receptor-positive cancers. The trial randomized 5157 women recurrence-free at 5 years to letrozole or placebo. A case-control design was adopted owing to challenges in obtaining archived tumor samples. An eligible case (319 of which 83 were examined) was one that experienced a local, regional, or distant recurrence and had an available tumor sample. Two controls free of recurrence longer than cases were matched to each case based on age, tumor size, node status, and prior chemotherapy. Any recurrence (local, regional, or distant) was used as the end point; patients with contralateral or unknown recurrences were excluded. Using the 2-gene expression H/I ratio, which is obtained from the BCI, there was a 42% relative risk reduction in the low-risk group vs a 77% reduction in the high-risk group. Although statistical significance was lacking in the low-risk group, the CIs were wide and included values consistent with those observed in the high-risk group (see Table 16).

Zhang et al (2013) also reported a larger potential relative risk reduction in the high-risk group of the Stockholm trial, with similar uncertainty reflected in the CIs (see Table 17).

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Comparators</th>
<th>Low Risk</th>
<th>High Risk</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sgroi et al (2013)</td>
<td>249</td>
<td>Letrozole vs placebo</td>
<td>HR (95% CI) 0.58 (0.25 to 1.36)</td>
<td>ARR 4% HR (95% CI) 0.33 (0.15 to 0.73)</td>
<td>Nested matched CC study; 83 recurrences in 166 controls; 5-y ARRs reported Stockholm trial, 15-y results</td>
</tr>
<tr>
<td>Zhang et al (2013)</td>
<td>600</td>
<td>Tamoxifen vs placebo</td>
<td>HR (95% CI) 0.67 (0.36 to 1.24)</td>
<td>ARR 4.9% HR (95% CI) 0.35 (0.19 to 0.65)</td>
<td>19.6%</td>
</tr>
</tbody>
</table>


Clinical Utility

No decision-impact studies were identified that report clinical outcomes such as survival or recurrence. No studies comparing genetic test classifications with clinical risk prediction tools were identified. Two studies provided evidence for the clinical validity of the BCI Prediction. Wide CIs in the results do not support the clinical utility of this test in identifying women who can safely forgo extended endocrine therapy.

Section Summary: Breast Cancer Index (Prognosis and Prediction)

Three studies analyzing data from 2 Simon category B studies and 1 Simon category C study evaluated the BCI Prognosis for women who are recurrence-free for 5 years considering extended endocrine therapy. The 10-year distant recurrence rates were significantly low, and the 10-year distant recurrence-free survival estimates were significantly high for patients identified by the BCI as low risk. The studies evaluating the BCI Prediction reported results with wide CIs, indicating uncertainty in distinguishing between the low- and high-risk groups.

MammaPrint (70-Gene Signature)

Clinical Validity

Esserman et al (2017) conducted a secondary analysis on data from women who were node-negative, participating in an RCT of tamoxifen vs no systemic therapy, with over 20 years of follow-up (Stockholm tamoxifen trial, STO-3). This is a Simon category B study. A total of 652 tissue samples from the trial underwent MammaPrint risk classification, 313 from the tamoxifen arm and 339 from the no therapy arm. The primary outcome was 20-year BCSS. Initial classification by MammaPrint identified 58% of the patients as low risk for distant recurrence and 42% as high risk. Twenty-year BCSS rates were 85% and 74% (p<0.001), respectively. Analysis was
conducted on a subgroup of the low-risk group, considered ultralow risk. The tamoxifen-treated ultralow-risk group did not experience any deaths at 15 years. Survival rates were high for all patients in the ultralow-risk group, 97% for those treated with tamoxifen and 94% for those untreated. Table 18 details survival rates for the initial low- and high-risk groups, and for the subgroup analysis that separated an ultralow-risk group.

**Table 18. Ten- and 20-Year Follow-up Results by MammaPrint Risk Group**

<table>
<thead>
<tr>
<th>Study (Source of Patients)</th>
<th>N</th>
<th>MP Risk Score Group, N (%)</th>
<th>10-Year BCSS, % (95% CI)</th>
<th>20-Year BCSS, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esserman et al (2017)³³</td>
<td>652</td>
<td>Low risk: 377 (58) High risk: 275 (42)</td>
<td>90 (87 to 93) 81 (74 to 86)</td>
<td>85 (80 to 89) 74 (66 to 80)</td>
</tr>
<tr>
<td>Esserman et al (2017)³³</td>
<td>652</td>
<td>Ultralow risk: 98 (15) Low but not ultralow risk: 279 (43) High risk: 275 (42)</td>
<td>99 (92 to 100) 88 (83 to 91) 80 (75 to 85)</td>
<td>95 (86 to 99) 82 (76 to 86) 73 (67 to 79)</td>
</tr>
</tbody>
</table>

BCSS: breast cancer-specific survival; CI: confidence interval; MP: MammaPrint.

**Clinical Utility**

No decision-impact studies were identified that reported clinical outcomes such as survival or recurrence. One study provided evidence for the clinical validity of MammaPrint when a subgroup of the low-risk group, an ultralow-risk group, was identified, that can safely forgo extended endocrine therapy. However, no studies comparing genetic test classifications with clinical risk prediction tools were identified.

**Section Summary: MammaPrint**

One Simon category B study meeting inclusion criteria was identified. A subgroup of the low-risk patients was identified, and it showed high 10-year BCSS rates. Additional studies are needed to confirm the benefit of MammaPrint for identifying women who may forgo extended endocrine therapy. Studies comparing the genetic test to clinical prediction models are also needed.

**Prosigna**

**Clinical Validity**

Filipits et al (2014) analyzed data from patients in the ABCSG-8 trial (5 years of adjuvant tamoxifen vs tamoxifen for 2 years followed by anastrozole).⁵⁰ Adjuvant chemotherapy was not administered. The PAM50 ROR predecessor test of Prosigna was obtained from archival samples using the NanoString nCounter device. At 5 years, 1246 patients free of recurrence were included in the analyses (74% node-negative). Almost all patients (97%) classified as low risk were node-negative. Between years 5 and 15, there were 7 distant recurrences in the low-risk group (n=460) and none recorded among the 12 low-risk node-positive patients. The cumulative risk of late distant recurrence was 2.4% (95% CI, 1.1% to 5.3%). However, as of year 11, 59% of the low-risk group was being followed and at risk, and at year 14 just 11%. The authors also evaluated a clinical linear predictor score (age, grade, nodal status, endocrine treatment) but did not present recurrence rates by clinical risk categories (e.g., low, intermediate, high).

Sestak et al (2013) reported limited results concerning late recurrences obtained from patients in the ATAC trial who received anastrozole with tamoxifen alone or in combination.⁵² From a subset of women in the monotherapy arms with archived tissue (a sample forming the TransATAC study), a total of 940 U.K. women from the study were analyzed. Distant recurrence was the primary end point (censored at death). The sample included patients with node-positive and node-negative cancers, but proportions were not reported. There were 83 distant recurrences from years 5 to 10. A clinical treatment score derived from age, node status, treatment, stage, and grade was examined but its prognostic value not reported. Annualized hazards (distant recurrence rates) were consistent with a lower late recurrence risk for node-negative tumors 2 cm or smaller and among those with a low PAM50 ROR score. From a Kaplan-Meier plot, the late distant recurrence risk in the PAM50 ROR low-risk group was estimated at 4.1% (CIs were not
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displayed). The absence of CIs and comparison or reclassification of clinical predictors' prognosis limits any conclusions.

A subsequent publication by Sestak et al (2015) combined samples of women with hormone receptor-positive, HER2-negative cancers from the ABSCG-8 and TransATAC studies included in the 2 prior publications. Risk was determined using both a Clinical Treatment Score (CTS; treatment received, positive nodes, tumor size, age, and grade) and the PAM50 ROR. As in the prior studies, death was considered a censoring event; women with recurrences through 5 years were excluded, and the median follow-up was 10 years. Approximately 25% of patients had positive nodes. Both the ROR and CTS were prognostic, but cumulative event rates reported only for the ROR (see Table 15). In the ROR low-risk group, the distant recurrence rate was 2.4% (95% CI, 1.6% to 3.5%) in all women and 2.0% (95% CI, 1.3% to 3.2%) when only node-negative patients were examined. Finally, the authors compared the ability of the ROR to reclassify patients with the CTS. From a reclassification analysis (see Table 19), assuming a selective as opposed to a treat-all strategy and that only low-risk women would not be treated: (1) adding the ROR to the CTS would have resulted in 5 (3.4%) more of 148 patients experiencing distant recurrence being treated, and (2) 60 (3.0%) of 1989 additional patients not experiencing a recurrence would have been incorrectly treated. The reclassification results would suggest caution when interpreting prognostic estimates without considering clinical predictors.25

Table 19. Classification and Reclassification Achieved by Adding Risk of Recurrence Score to the Clinical Treatment Score

<table>
<thead>
<tr>
<th>Distant Recurrence</th>
<th>CTS</th>
<th>CTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Int High</td>
<td>Total</td>
</tr>
<tr>
<td>ROR Low</td>
<td>18 14 0</td>
<td>32 ROR + CTS</td>
</tr>
<tr>
<td>Intermediate</td>
<td>7 31 7</td>
<td>45</td>
</tr>
<tr>
<td>High</td>
<td>8 17 46</td>
<td>71</td>
</tr>
<tr>
<td>Total</td>
<td>33 62 53</td>
<td>148</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No Distant Recurrence</th>
<th>CTS</th>
<th>CTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Int High</td>
<td>Total</td>
</tr>
<tr>
<td>ROR Low</td>
<td>837 273 41</td>
<td>1151 ROR + CTS</td>
</tr>
<tr>
<td>Intermediate</td>
<td>209 221 63</td>
<td>493</td>
</tr>
<tr>
<td>High</td>
<td>60 137 148</td>
<td>345</td>
</tr>
<tr>
<td>Total</td>
<td>1106 631 252</td>
<td>1989</td>
</tr>
</tbody>
</table>

CTS: Clinical Treatment Score; Int: intermediate; ROR: risk of recurrence.

Clinical Utility

No decision-impact studies were identified that report clinical outcomes such as survival or recurrence. Limitations (e.g., lack of reporting recurrence rates by ROR categories, lack of CIs) in the studies that evaluated clinical validity preclude any conclusions for clinical utility of this test for this indication. One study compared genetic test classifications with a clinical risk prediction tool and reported minimal improvement of the test over the clinical prediction tool.

Section Summary: Prosigna

Studies obtained from 2 completed trials analyzed in different publications (2 Simon category B studies) have found that the PAM50 ROR can identify patients at low risk of late distant recurrence. However, a reclassification result suggested that the test may offer little improvement over clinical predictors alone.

Section Summary: Extended Endocrine Therapy Beyond 5 Years

At least 3 randomized controlled trials have demonstrated survival improvements with extended tamoxifen. While the evidence for extended aromatase inhibitor is more mixed than the other trials, guidelines have recommended extended endocrine therapy with tamoxifen or an aromatase inhibitor in all hormone receptor-positive women. However, 3 trials completed and presented in 2017 but not yet published (described in the Background section) may challenge a
“treat-all” approach. Results of these trials may affect the uncertainty in possible benefit and the impact on treatment strategies.

Compared with the choice of adjuvant chemotherapy depending on baseline recurrence risk, there is less empirical research on women’s threshold for decision-making to forgo extended endocrine therapy based on recurrence risk. To be clinically useful, a test should be able to predict accurately a cumulative lifetime recurrence rate in a range that would be meaningful for decision-making.

If one assumes, as suggested by the studies reviewed, that the predicted 10-year or later distant recurrence rates would be sufficiently lower than 10%, then according to the Simon levels of evidence, the BCI and Prosigna have 2 category B studies appropriately reported to support their use. However, evidence demonstrating incremental reclassification improvement applying decision informative thresholds is lacking. The single reclassification result does not offer strong support for net incremental improvement, particularly if the way in which women value benefits (net improvement in those recurrences) and harms (increased false positives in those without recurrences) is considered.

Moreover, it is not readily apparent how the test result informs decision-making at the time results are available.

**Test Comparison Studies**

Bosl et al (2017) compared MammaPrint with EndoPredict in 48 tumor samples—29 were node-negative, and 19 were node-positive.56 For the MammaPrint test, RNA quality was low for 3 samples. Of the 45 tested by MammaPrint, 17 (38%) were classified as low risk, and 28 (62%) were classified as high risk for recurrence. Four samples were excluded from the EndoPredict analysis because the tumors were estrogen receptor-positive or HER2-positive, which are not part of the inclusion criteria of this test. Based on the EP molecular score, 8 (18%) samples were classified as low risk, and 36 (82%) samples were classified as high risk. Based on the EPclin score, 17 (39%) samples were considered low risk, and 27 (61%) samples were considered high risk. There was no statistically significant agreement between MammaPrint and molecular EP (overall concordance, 63%) or between MammaPrint and EPclin (overall concordance, 66%).

Sgroi et al (2013) compared the BCI with Oncotype DX in 665 lymph node-negative women receiving endocrine therapy but not chemotherapy in the ATAC trial.31 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, the BCI was a better predictor of risk: 5% of the BCI low-risk patients had distant recurrence compared with 9% of Oncotype DX low-risk patients, and 22% of the BCI high-risk patients had distant recurrence compared with 13% of Oncotype DX high-risk patients. These values were reported without 95% CIs; it is therefore not possible to assess the degree of overlap between risk groups.

Sestak et al (2016)57 examined cross-stratification between the BCI and Oncotype DX RS using the same data as Sgroi et al (2013).31 Patients from the ATAC trial (N=665) who were postmenopausal, hormone receptor-positive, and node-negative were included. Median follow-up was 10 years. Gene expression analyses for both scores were conducted, and risk categories were determined based on prespecified cutoff points (RS: <18=low risk, 18-31=intermediate risk, >31=high risk; BCI: <5.0825=low risk, 5.0825-6.5025=intermediate risk, >6.5025=high risk). Each gene expression score was combined with the CTS an algorithm of nodal status, tumor size, grade, age, and treatment. In a multivariate analysis, when the BCI was added to RS plus CTS, there was a significant effect on prognostic information. When RS was added to the BCI plus CTS, no additional prognostic information was added.
Dowsett et al (2013) compared the PAM50 ROR score with the Oncotype DX 21-gene RS and IHC4 breast cancer algorithm. 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 CTS. Statistical testing of these parameters was significant and favored the ROR score over the RS. More patients were classified as high-risk and fewer as intermediate risk by the ROR than by RS. Prognostic information provided by the 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 Oncotype DX RS (n=31), MammaPrint (n=14), Adjuvant! Online (n=12), 5-antibody immunohistochemical (IHC) panel (Mammostrat; n=3), and a 14-gene signature (BreastOncPx; n=1). Oncotype DX RS satisfied level 1 evidence for estimating distant recurrence risk, 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 I or II 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 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 Oncotype DX, 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 distant metastasis-free survival 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). There was slightly more variation in distant metastasis-free survival, explained by the combination of the 21-gene RS plus either Adjuvant! Online (25.8, SD=1.4) or the Nottingham Prognostic Index (23.7, SD=1.5) as opposed to the combination of the 70-gene signature plus Adjuvant! Online (23.1, SD=1.2) or the Nottingham Prognostic Index (22.4, SD=1.3). However, differences were small and any combination was significantly better than any test or clinicopathologic classifier alone.

Two studies have compared Oncotype DX with 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,
Additional Applications and Other Tests

Based on a 2008 study that compared Oncotype DX estrogen and progesterone receptor results with traditional IHC results, Genomic Health 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 the quantitative estrogen receptor by Oncotype DX was more strongly associated with disease recurrence than the 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 the IHC and Oncotype DX for progesterone receptor status ($\rho=0.91$) than for estrogen receptor status ($\rho=0.65$), but worse concordance (at various cut points) for progesterone receptor status (99%) than for estrogen receptor status (88).64

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) used MammaPrint to assess 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 radiotherapy and did not receive adjuvant chemotherapy; approximately half of the patients received adjuvant endocrine therapy. At a 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 vs 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 (i.e., 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 a median follow-up of 6 years, the Kaplan-Meier estimate for 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 vs 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, either by providing more aggressive treatment to high-risk patients or by providing less aggressive treatment to low-risk patients, is not clear.

Summary of Evidence

Early-Stage Node-Negative Invasive Breast Cancer

For the evaluation of breast cancer–related gene expression profiling tests for the management of all early-stage breast cancer populations, study populations considered had positive...
hormone receptor status, and negative HER2 status. Studies retrospectively collecting tumor samples from prospective trials that provide 10-year distant recurrence rates or 10-year survival rates in node-negative women not receiving adjuvant chemotherapy were included in this part of the evidence review.

**Oncotype DX (21-Gene Assay)**

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with Oncotype DX (21-gene assay), 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 reasonable (average risk at 10 years, 3%-7%; upper bound of the 95% CI, 6% to 10%). 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 revealed that a low score was associated with a low absolute risk of 10-year distant recurrence (average risk at 10 years for the 2 larger studies, 3%-6%; upper bound of the 95% CI, 6% to 9%). Over half of patients in these 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, the evidence includes findings from 2 prospective-retrospective studies and a registry-based observational study. The findings from the 2 prospective-retrospective studies showed that a low-risk Breast Cancer Index score is associated with low 10-year distant recurrence rates (average risk at 10 years, 5%-7%; upper bound of the 95% CI, 8% to 10%). 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.

**MammaPrint (70-Gene Signature)**

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with MammaPrint (70-gene signature), the evidence includes a prospective-retrospective study and a study using a cancer registry cohort. The prospective-retrospective study reported high 10-year distant metastases-free survival for the low-risk group treated with tamoxifen (93%, 95% CI, 88% to 96%), but not as high survival for the low-risk group not treated with tamoxifen (83%, 95% CI, 76% to 88%). Although the registry study showed a low risk of 10-year distant recurrence, the source is not considered high-quality. Although MammaPrint tends to stratify patients into categories with different outcomes, research continues 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. A recently reported study of clinical utility only reported 5-year results and may not identify a group with sufficiently low risk.

**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 (average
risk at 10 years, 3%-5%; upper bound for the study providing CI, 6%). 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 decisions on management of early-stage node-positive disease, Oncotype DX, EndoPredict, MammaPrint, and Prosigna were evaluated. Only studies presenting 10-year distant recurrence rates or 10-year survival rates were included in this part of the evidence review.

**Oncotype DX (21-Gene Assay)**

For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with Oncotype DX (21-gene assay), the evidence includes 2 prospective-retrospective studies and a prospective study. The prospective-retrospective studies showed that Oncotype DX stratifies node-positive patients into high and low risk for distant recurrence-free survival. However, only one of the studies reported CIs for estimates and those are very wide. The prospective study included patients with node-negative and node-positive breast cancer. The authors reported that subgroup analyses of patients with node-positive breast cancer who were classified as low risk experienced higher rates of survival than patients classified as high risk, though no rates were provided. There is a wide range of survival improvements over which individual patients would elect or refuse adjuvant chemotherapy, but accurate risk estimates are needed to inform patient decisions. The evidence is insufficient to determine the effects of the technology on health outcomes.

**EndoPredict**

For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with EndoPredict, the evidence includes 2 prospective-retrospective analyses. In a study, the 10-year distant recurrence rate in low-risk EPclin score patients was estimated to be 5% (95% CI, 1% to 9%). In the other study, 10-year distant recurrence rate in low-risk EPclin score patients was estimated to be 5% but the upper bound of the 95% CI was close to 20%. To establish that the test has potential for clinical utility, it should be able to identify a low-risk group with a recurrence risk that falls within a range that is clinically meaningful for decision-making about avoiding adjuvant chemotherapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

**MammaPrint (70-Gene Signature)**

For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with MammaPrint (70-gene signature), the evidence includes a clinical utility study and an observational study. The study of clinical utility only reported 5-year results and may not identify a group with sufficiently low risk. The observational study reported that the low-risk group experienced a low rate of 10-year distant recurrence; however, the standard error around the rate did not meet the threshold benefit of less than 10%. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Prosigna**

For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with the Prosigna ROR score, the evidence includes a single prospective-retrospective study. The 10-year distant recurrence rate in low-risk Prosigna ROR patients with a single positive node is roughly twofold the rate in low-risk ROR score node-negative patients. However, in the single available study, the upper bound of the 95% CI for 10-year distant recurrence in node-positive patients classified as ROR score low-risk was about 13%, which approaches the range judged clinically informative in node-negative patients. The predicted recurrence rates require replication. To establish that the test has potential for clinical utility, it should be able to identify a low-risk group with a recurrence risk that falls within a range that is clinically meaningful for decision-making about avoiding adjuvant
chemotherapy. 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 DCIS.

**Oncotype DX Breast Ductal Carcinoma In Situ Score**
For individuals who have DCIS considering radiotherapy who receive gene expression profiling with the Oncotype DX Breast DCIS Score, the evidence includes a prospective-retrospective study and a retrospective cohort study. Although the 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 a 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.

**Extended Endocrine Therapy**
For this indication, Oncotype DX, EndoPredict, Breast Cancer Index, MammaPrint, and Prosigna were evaluated. Studies retrospectively collecting tumor samples from prospective trials that provided 10-year distant recurrence rates or 10-year survival rates were included in this part of the evidence review. Studies comparing genetic assays with clinical risk prediction tools were also included.

**Oncotype DX (21-Gene Assay)**
For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending endocrine treatment who receive gene expression profiling with Oncotype DX (21-gene assay), the evidence includes a study from a previously conducted clinical trial. The study did not show low distant recurrence rates in patients classified as low risk with the test, and no CIs were presented. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. The evidence is insufficient to determine the effects of the technology on health outcomes.

**EndoPredict**
For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending endocrine treatment who receive gene expression profiling with EndoPredict, the evidence includes a study of archived tissue samples from a previously conducted clinical trial. The study showed low distant recurrence rates in patients classified as low risk with EndoPredict. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. Additional prospective trials or retrospective-prospective studies of archived samples reporting on the association between risk score and survival are needed for confirmation of results from the single study. More importantly, clarity is needed about how the test would inform clinical practice. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Breast Cancer Index**
For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending tamoxifen treatment who receive gene expression profiling with the Breast Cancer Index, the evidence includes 3 analyses of archived tissue samples from two previously conducted clinical trials and a retrospective cohort study. The analyses showed low distant recurrence rates and high distant recurrence-free survival rates in patients classified as low risk with the test. Two studies suggested that, in addition to having a more favorable prognosis, low-risk patients may receive less benefit from extended endocrine therapy. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. Clarity about how the test would inform clinical practice is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.
MammaPrint (70-Gene Signature)
For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending tamoxifen treatment who receive gene expression profiling with MammaPrint (70-gene signature), the evidence includes a retrospective-prospective study. Analyses on patients classified as ultralow risk (a subgroup of the low-risk group) showed that this ultralow-risk group experienced high 10- and 20-year breast cancer-specific survival rates. Additional studies are needed to confirm the results of this single study. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. Clarity about how the test would inform clinical practice is needed. 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 who are distant recurrence-free at 5 years who are considering extending tamoxifen treatment who receive gene expression profiling with Prosigna, the evidence includes 2 studies from previously conducted clinical trials examined in 3 publications. The studies showed low distant recurrence rates in patients classified as low risk with the test. A reclassification result suggested that the test may offer little improvement over clinical predictors alone. Clarity about how the test would inform clinical practice is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
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 from Blue Cross Blue Shield Association, input was received from 1 physician specialty society and 4 academic medical centers in 2008. A clear majority of reviewers agreed with the policy conclusions.

Practice Guidelines and Position Statements
National Comprehensive Cancer Network
Guidelines from the National Comprehensive Cancer Network (NCCN; v.2.2017) recommend the use of the 21-gene reverse transcriptase polymerase chain reaction (RT-PCR) assay for determining the use of adjuvant chemotherapy in patients with the following tumor characteristics:
- Hormone receptor-positive
- Human epidermal growth factor receptor 2 (HER2)-negative
- Ductal, lobular, mixed, or metaplastic histology
- “pT1, pT2, or pT3 stage; and pN0 or pN1mi (≤2 mm axillary node metastasis)”
- Tumor >0.5 cm

The guidelines also state: “The 21-gene RT-PCR assay recurrence score can be considered in select patients with 1 to 3 involved ipsilateral axillary lymph nodes to guide the addition of combination chemotherapy to standard hormone therapy. A retrospective analysis of a prospective randomized trial suggests that the test is predictive in this group similar to its performance in node-negative disease.”

Further, the NCCN guidelines state: “The NCCN Panel members acknowledge that many assays have been clinically validated for prediction of prognosis. However, based on the currently available data, the panel believes that the 21-gene assay has been best validated for its use as
a prognostic test as well as in predicting who is most likely to respond to systemic chemotherapy.”

Other tests mentioned and studies reviewed in the NCCN guidelines included MammaPrint and Prosigna. NCCN guidelines state that “Other prognostic multigene assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy.”

**American Society of Clinical Oncology**
In 2017, the American Society of Clinical Oncology updated its evidence-based guidelines on the use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer. The guidelines did not endorse any test for decision-making to determine the length of tamoxifen treatment.

**European Group on Tumor Markers**
In 2017, the European Group on Tumor Markers updated its guidelines on the clinical use of biomarkers in breast cancer. Table 21 summarizes guidelines on the use of biomarkers in patients with invasive breast cancer.

<table>
<thead>
<tr>
<th>Test</th>
<th>Recommendation</th>
<th>LOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncotype DX</td>
<td>For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy in patients with ER-positive/HER2-negative, lymph node-negative and lymph node-positive (1 to 3 nodes) disease</td>
<td>1B</td>
<td>A</td>
</tr>
<tr>
<td>MammaPrint</td>
<td>For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy to patients with ER-positive/HER2-negative, lymph node-negative and lymph node-positive (1 to 3 nodes) disease</td>
<td>1A</td>
<td>A</td>
</tr>
<tr>
<td>Prosigna</td>
<td>For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy to patients with ER-positive/HER2-negative, lymph node-negative and lymph node-positive (1 to 3 nodes) disease</td>
<td>1B</td>
<td>A</td>
</tr>
<tr>
<td>EndoPredict</td>
<td>For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy to patients with ER-positive/HER2-negative, lymph node-negative and lymph node-positive (1 to 3 nodes) disease</td>
<td>1B</td>
<td>A</td>
</tr>
<tr>
<td>Breast Cancer Index</td>
<td>For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy in patients with ER-positive/HER2-negative, lymph node-negative disease</td>
<td>1B</td>
<td>A</td>
</tr>
</tbody>
</table>

ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; LOE: level of evidence; SOR: strength of recommendation.

**St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer**
The 2015 St. Gallen expert panel focused on “providing a practical approach to the allocation of available therapies” based on “tumor factors … such as hormone receptors and HER2 status, and the metastatic potential, as reflected in measures of proliferation and anatomic extent of disease [and p]atient factors [such as] menopausal status, age, comorbidity, and patient preference.”

“Oncotype DX®, MammaPrint®, PAM-50 ROR® score, EndoPredict®, and the Breast Cancer Index® were all considered usefully prognostic for years 1-5. Beyond 5 years, the Panel was divided almost equally on the prognostic value of Oncotype DX®, EndoPredict®, and the Breast Cancer Index. PAM50 ROR® score was agreed to be clearly prognostic beyond 5 years, and a clear majority rejected the prognostic value of MammaPrint® in this time period. Only Oncotype DX® commanded a majority in favor of its value in predicting the usefulness of chemotherapy.”
The St. Gallen International Expert panel reconvened in 2017 and their final report is pending.

The Panel noted that threshold values for decision-making about cytotoxic chemotherapy in patients with luminal disease had not been established for any of the tests. "Multi-parameter molecular assays are expensive and therefore unavailable in much of the world."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, decisions are left to the discretion of local Medicare carriers.

In November 2014, Palmetto GBA issued a local coverage determination for the Breast Cancer Index. Effective October 1, 2015, the policy limits coverage of the Breast Cancer Index to patients who meet all of the following criteria:

- Post-menopausal female with non-relapsed, ER+ [estrogen receptor] breast cancer
- Is lymph node negative
- Is completing 5 years of tamoxifen therapy
- Patient must be eligible for consideration of extended endocrine therapy based on published clinical trial data or practice guidelines
- Physician or patient is concerned about continuing anti-hormonal therapy because of documented meaningful toxicity or possible significant patient-specific side effects
- The test results will be discussed with the patient (including the limitations of the testing method, the risks and benefits of either continuing or stopping the therapy based on the test, and current cancer management guidelines)

Ongoing and Unpublished Clinical Trials
Current ongoing and unpublished trials that might influence this review are listed in Table 22.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01501487</td>
<td>MINT: Multi-Institutional Neo-Adjuvant Therapy MammaPrint Project</td>
<td>226</td>
<td>Jun 2017 (ongoing)</td>
</tr>
<tr>
<td>NCT00310180</td>
<td>Program for the Assessment of Clinical Cancer Tests (PACCT-1): Trial Assigning Individualized Options for Treatment: The TAILORx Trial</td>
<td>11,248</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>NCT02627703</td>
<td>A Prospective Clinical Utility Study of the Impact of the 21-Gene Recurrence Score Assay (Oncotype DX) in Estrogen Receptor Positive (ER+) HER 2 Negative (HER2-) 1-3 Node Positive (pN1) Breast Cancer in Multiple BC Cancer Agency Centres</td>
<td>80</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>NCT02395575</td>
<td>Prospective Study Evaluating the Clinical Impact of the Breast Cancer Intrinsic Subtype-Prosigna Test (Assay) in the Management of Early Stage Breast Cancers</td>
<td>200</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>NCT00433589</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>
</tr>
<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 more</td>
<td>10,000</td>
<td>Feb 2022</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>NCTNo.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02653755a</td>
<td>Less RxPONDER: A Clinical Trial Rx for Positive Node, Endocrine Responsive Breast Cancer</td>
<td>1380</td>
<td>Jun 2023</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

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Appendix

Appendix Table 1. Categories of Genetic Testing

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual's germline to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>1a. Diagnostic</td>
<td></td>
</tr>
<tr>
<td>1b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>1c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>2a. Diagnostic</td>
<td>X</td>
</tr>
<tr>
<td>2b. Prognostic</td>
<td>X</td>
</tr>
<tr>
<td>2c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
<td></td>
</tr>
<tr>
<td>4. Testing of an affected individual's germline to benefit family members</td>
<td></td>
</tr>
<tr>
<td>5. Reproductive testing</td>
<td></td>
</tr>
<tr>
<td>5a. Carrier testing: preconception</td>
<td></td>
</tr>
<tr>
<td>5b. Carrier testing: prenatal</td>
<td></td>
</tr>
<tr>
<td>5c. In utero testing: aneuploidy</td>
<td></td>
</tr>
<tr>
<td>5d. In utero testing: familial variants</td>
<td></td>
</tr>
<tr>
<td>5e. In utero testing: other</td>
<td></td>
</tr>
<tr>
<td>5f. Preimplantation testing with in vitro fertilization</td>
<td></td>
</tr>
</tbody>
</table>

Appendix 1. Study Selection Criteria by Specific Indications

Early-Stage Node-Negative Invasive Breast Cancer—Adjuvant Chemotherapy Decisions

Blue Cross Blue Shield Association required that distant disease recurrence be presented in node-negative, estrogen receptor-positive patients untreated with adjuvant chemotherapy. Results including only human epidermal growth factor receptor 2 (HER2)-negative patients were preferred, but many studies included small proportions of HER2-positive patients, which should not severely affect the findings. Exceptions to these selection criteria are noted. Studies presenting 10-year distant disease recurrence rates were selected. Blue Cross Blue Shield Association additionally selected recently published prospective studies specifically designed to evaluate the clinical utility of genetic expression profiles, even though these studies have only reported 5-year distant disease recurrence rates.

Blue Cross Blue Shield Association excluded studies in which the gene expression algorithm was being developed (“training sets”) and studies using convenience samples of patients. Blue Cross Blue Shield Association also excluded studies in different populations and for different outcomes that may contribute to the body of evidence for the capability of the tests to improve the prediction of prognosis.

Early-Stage Node-Positive Invasive Breast Cancer—Adjuvant Chemotherapy Decisions

For studies evaluating prognosis, Blue Cross Blue Shield Association required that 10-year outcomes (distant disease recurrence, disease-free survival, or overall survival) be presented in node-positive, estrogen receptor-positive patients untreated with adjuvant chemotherapy. In addition, any studies specifically prospectively designed to evaluate the clinical utility of genetic expression profile algorithms were selected. Blue Cross Blue Shield Association excluded studies in which the gene expression algorithm was being developed (“training sets”) and studies using convenience samples of patients. Blue Cross Blue Shield Association also excluded studies in different populations and for different outcomes that may contribute to the body of evidence for the capability of the tests to improve the prediction of prognosis.
expression profiles with reported 5-year outcomes were included. Blue Cross Blue Shield
Association excluded studies in which the gene expression algorithm was being developed
(“training sets”) and studies using convenience samples of patients.

**Extended Endocrine Therapy Decisions**

For studies evaluating prognosis, Blue Cross Blue Shield Association required that late (5 to 10
years or beyond) recurrences (distant disease recurrence, disease-free survival, or overall
survival) be presented in estrogen receptor-positive patients. Blue Cross Blue Shield Association
excluded studies in which the gene expression algorithm was being developed (“training sets”) and studies using convenience samples of patients.

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12. Stewart HJ, Prescott RJ, Forrest AP. Scottish adjuvant tamoxifen trial: a randomized study


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Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Reason for test and whether the test will help guide treatment decision regarding chemotherapy
  - Breast tumor size and classification, node status, differentiation and/or unfavorable features
  - HER2 status
  - Hormone receptor status
- Operative report(s): breast surgery
- Pathology report(s)
- Laboratory report including: specific name and test requested (HER2, Hormone receptor status)

Post Service

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms.
of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**
The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CPT®</strong></td>
<td>0008M</td>
<td>Oncology (breast), mRNA analysis of 58 genes using hybrid capture, on formalin-fixed paraffin-embedded (FFPE) tissue, prognostic algorithm reported as a risk score <em>(Deleted code effective 1/1/2018)</em></td>
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<td>0045U</td>
<td>Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score <em>(Code effective 7/1/2018)</em></td>
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<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
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<td>81519</td>
<td>Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score</td>
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<td>81520</td>
<td>Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score <em>(Code effective 1/1/2018)</em></td>
</tr>
<tr>
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<td>81521</td>
<td>Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis <em>(Code effective 1/1/2018)</em></td>
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<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
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<td><strong>HCPCS</strong></td>
<td>S3854</td>
<td>Gene expression profiling panel for use in the management of breast cancer treatment</td>
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<td><strong>ICD-10</strong></td>
<td>None</td>
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**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>12/01/2005</td>
<td>New Policy Adoption</td>
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<tr>
<td>03/12/2007</td>
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<td>04/03/2009</td>
<td>Policy Revision</td>
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</tr>
<tr>
<td>01/11/2013</td>
<td>Policy revision with position change</td>
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<tr>
<td>01/23/2013</td>
<td>Coding update</td>
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<tr>
<td>09/27/2013</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
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<tr>
<td>09/30/2014</td>
<td>Policy title change from Gene Expression Profiling for Managing Breast Cancer Treatment Policy revision with position change</td>
<td>Medical Policy Committee</td>
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Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer

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<tr>
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<td>07/01/2016</td>
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<td>07/01/2018</td>
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<td>09/01/2018</td>
<td>Coding update</td>
<td>Administrative Review</td>
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</table>

Definitions of Decision Determinations

**Medically Necessary**: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental**: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation**: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.