Medical Policy

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

Professional

Original Effective Date: July 1, 2007
Revision Date(s): November 9, 2011;
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Populations	Interventions	Comparators	Outcomes
Individuals: • With early-stage node-negative invasive breast cancer considering adjuvant chemotherapy	Interventions of interest are: • Gene expression profiling with Oncotype DX (21-gene signature)	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: Disease-specific survival Change in disease status

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Individuals: • With early-stage node-negative invasive breast cancer considering adjuvant chemotherapy	Interventions of interest are: • Gene expression profiling with EndoPredict	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With early-stage node-negative invasive breast cancer considering adjuvant chemotherapy	Interventions of interest are: • Gene expression profiling with the Breast Cancer Index	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With early-stage node-negative invasive breast cancer considering adjuvant chemotherapy	Interventions of interest are: • Gene expression profiling with MammaPrint (70-gene signature)	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With early-stage node-negative invasive breast cancer considering adjuvant chemotherapy	Interventions of interest are: • Gene expression profiling with Prosigna	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With early-stage node-positive invasive breast cancer considering adjuvant chemotherapy	Interventions of interest are: • Gene expression profiling with Oncotype DX (21-gene signature)	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
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Individuals: • With ductal carcinoma in situ considering radiotherapy	Interventions of interest are: • Gene expression profiling with the Oncotype DX Breast DCIS Score	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Change in disease status
Individuals: • With early-stage node-negative invasive breast cancer, recurrence-free at 5 years, considering extended endocrine therapy	Interventions of interest are: • Gene expression profiling with Oncotype DX (21-gene signature)	Comparators of interest are: Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With early-stage node-negative invasive breast cancer, recurrence-free at 5 years,	Interventions of interest are:	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status

Populations	Interventions	Comparators	Outcomes
considering extended endocrine therapy	• Gene expression profiling with EndoPredict		
Individuals: • With early-stage node-negative invasive breast cancer, recurrence-free at 5 years, considering extended endocrine therapy	Interventions of interest are: • Gene expression profiling with the Breast Cancer Index	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With early-stage node-negative invasive breast cancer, recurrence-free at 5 years, considering extended endocrine therapy	Interventions of interest are: • Gene expression profiling with MammaPrint (70-gene signature)	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With early-stage node-negative invasive breast cancer, recurrence-free at 5 years, considering extended endocrine therapy	Interventions of interest are: • Gene expression profiling with Prosigna	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status

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. This report summarizes the evidence of 5 tests, which are organized by indication: Oncotype DX, EndoPredict, Breast Cancer Index, MammaPrint, and Prosigna.

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

OBJECTIVE

The objective of this policy is to determine whether Oncotype DX, EndoPredict, Breast Cancer Index, MammaPrint, and Prosigna testing improve the net health outcome among women making decisions about breast cancer treatment.

BACKGROUND

Newly Diagnosed Breast Cancer

Most women with newly diagnosed breast cancer in the United States present with early-stage or locally advanced (ie, 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 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 to 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 (NCCN) recommend extended endocrine therapy.[2] The American Society for Clinical Oncology's (ASCO) 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 7-8 to 10 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 (ie, cancer extending beyond the basement membrane of the mammary ducts into adjacent tissue), adjuvant cytotoxic chemotherapy consistently provides approximately a 30% relative risk reduction in 10-year breast cancer mortality regardless of 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 to negative (Table 1 shows recurrence risk for estrogen receptor–positive cancers for patients followed in the International Breast Cancer Study Group).[1] Patients may have received no adjuvant treatment, or adjuvant tamoxifen and/or adjuvant chemotherapy.) These women have an approximately 15% ten-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 (eg, 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.[5] 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

	Recurrence, Hazard[a] (SE), %				
	Years				
Nodes	0-5	5-10	10-15	15-20	20-25
0	5.8 (0.5)	3.3 (0.4)	2.0 (0.4)	2.1 (0.4)	1.1 (0.4)
1 to 3	9.5 (0.6)	5.8 (0.6)	3.0 (0.5)	3.5 (0.7)	1.5 (0.6)
≥4	17.2 (0.9)	10.9 (1.2)	5.9 (1.2)	3.8 (1.2)	1.3 (0.9)
Size					
≤2 cm	7.0 (0.4)	4.8 (0.4)	2.9 (0.4)	2.7 (0.5)	1.5 (0.5)
>2 cm	12.9 (0.6)	6.1 (0.6)	2.9 (0.5)	2.7 (0.5)	1.1 (0.5)
Grade					
1	5.8 (0.6)	4.9 (0.7)	3.6 (0.7)	4.0 (0.9)	0.7 (0.5)
2	9.6 (0.5)	6.3 (0.5)	2.8 (0.4)	2.7 (0.5)	1.8 (0.5)
3	14.1 (0.8)	4.1 (0.6)	2.5 (0.6)	2.4 (0.7)	0.4 (0.4)

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]

Early randomized trials of extended tamoxifen treatment—Tormey et al (1996; total N=194 patients),[7] the National Surgical Adjuvant Breast and Bowel Project (Fisher et al [2001]; total N=1172 patients),[8] and the Scottish Cancer Trials Breast Group (Stewart et al [2001]; total N=342 patients)[9]—had mixed findings. However, more recent available trial evidence suggests that 10 years of tamoxifen in pre- or postmenopausal women can be linked with improved survival (see Table 2).

These randomized controlled trials have shown that extended endocrine therapy decreases the risk of recurrence. The ATLAS trial, which compared 5 and 10 years of tamoxifen,[10] and the subsequent aTTom trial (reported in abstract form)[11] included women who were hormone receptor–positive who had completed 5 years of tamoxifen. Five years of extended tamoxifen was associated with improvements in breast cancer–specific mortality in both ATLAS and ATTom; however, only ATLAS showed improvements in overall survival (see Table 2).

Several trials have compared survival outcomes in women using extended aromatase inhibitors vs placebo following several years of tamoxifen,[12-15] and 2 trials compared the use of extended aromatase inhibitors for different durations (3 years vs 6 years[16] and 2.5 years vs 5 years[17]) (see Table 2). No differences in overall survival were detected between the aromatase inhibitor groups and with the placebo groups. Differences in breast cancer–specific survival were inconsistent. Differences in disease specific survival and overall survival were not detected among patients receiving aromatase inhibitors for different lengths of time.

Guidelines for Extended Endocrine Therapy
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 the initial 5 years following initial diagnosis has support in national guidelines.[2,3,18] Support for extended endocrine therapy beyond the initial 5 years is inconsistent across various guidelines.

The latest guidelines from the American Society for Clinical Oncology (2014) discuss extended endocrine therapy for breast cancer have recommended an additional 5 years of tamoxifen for premenopausal women and 5 years of aromatase inhibitors for postmenopausal women.[4] National Comprehensive Cancer Network guidelines (v.2.2018) do not recommend extended endocrine therapy, but state that aromatase inhibitors or tamoxifen may be considered following 5 years of endocrine therapy. The guidelines also note that the optimal duration of aromatase inhibitors is uncertain.[2]

Adverse Events from Extended Endocrine Therapy
Adverse events from extended tamoxifen include increased risk of thromboembolic disease (deep vein thrombosis, pulmonary embolism) and endometrial cancer. The ATLAS trial reported relative risks of 1.9 (95% CI, 1.1 to 3.1) for pulmonary embolus and 1.7 (95% CI, 1.3 to 2.3) for endometrial cancer. Adverse events from extended aromatase inhibitors include musculoskeletal side effects (eg, carpal tunnel syndrome, bone pain, bone fractures). In meta-analyses comparing tamoxifen and aromatase inhibitors, results showed an increased risk in cardiovascular events with aromatase inhibitors relative to tamoxifen.[19,20] Women treated with aromatase inhibitors have also experienced higher fracture rates compared with women treated with tamoxifen.[21]

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

Study	Population	Comparators	Breast Cancer–Specific Mortality		Overall Mortality	
			Event RR (95% CI)	p	Event RR (95% CI)	p
Extended tamoxifen						
ATLAS (2013)[10]	6846 women with ER-positive, early breast cancer, after 5 y of TAM	Continue TAM to 10 y (n=3428) vs stop TAM at 5 y (n=3418)	• 0.83 (0.72 to 0.96) (331/3428 vs 397/3418)	0.01	• 0.87 (0.78 to 0.97) • 722 (639/3428 vs 722/3418)	0.01
aTTom (2013)[11]	6953 women with ER-positive or untested breast cancer, after 5 y of TAM	Continue TAM to 10 y (n=3468) vs stop TAM at 5 y (n=3485)	10 years • 392/3468 intervention vs 442/3485 control Years 5-9 • 1.03 (0.84 to 1.27) After year 9 • 0.77 (0.64 to 0.92)	0.05	10 years • 849/3468 intervention vs 910/3485 control Years 5-9 • 1.05 (0.90 to 1.22) After year 9 • 0.86 (0.75 to 0.97)	0.1
Extended aromatase inhibitor						
ABCSG (2007)[12]	856 post-menopausal women with ER- and/or PR-positive breast cancer, after 5 y of TAM	Anastrozole for 3 y (n=386) vs no further therapy (n=466)			5 years • 10.3% anastrozole vs 11.7% control Event HR (95% CI) • 0.89 (0.59 to 1.34)	0.57
			Breast Cancer–Specific Survival		**Overall Survival**	
IDEAL (2018)[17]	1824 post-menopausal women with ER- and/or PR-positive early breast cancer, after 5 y endocrine therapy	Letrozole for 2.5 y (n=909) or 5 y (n=915)	Median 6.6 Years • 2.5 y: 82.0% • 5 y: 83.3%	0.5	Median 6.6 Years • 2.5 y: 89.4% • 5 y: 88.6%	NS
DATA (2017)[16]	1912 post-menopausal women with ER- and/or PR-positive early breast cancer, after 2-3 y TAM	Anastrozole for 3 y (n=955) or 6 y (n=957)	5 Years • 3 y: 79.4% • 6 y: 83.1%	0.06	5 Years • 3 y: 90.4% • 6 y: 90.8%	0.6
NSABP (2008)[15]	1598 post-menopausal women with ER- and/or PR-positive early breast cancer, after 5 y of TAM	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	48 Months • ITT: 91% exemestane vs 89% placebo	0.07		

Study	Population	Comparators	Breast Cancer–Specific Mortality		Overall Mortality	
		crossed over to exemestane after unblinding				
NCIC CTG MA.17 trial (2003, 2005)[13,14]	5187 post-menopausal women with ER- and/or PR-positive early breast cancer, after 5 y TAM	Continue letrozole to 10 y (n=2593) vs stop TAM at 5 y (n=2594)	48 Months • 94.4% letrozole vs 89.8% placebo Event HR • 0.58 (0.45 to 0.76)	<0.001	48 Months • 96% letrozole vs 94% placebo Event HR • 0.76 (0.48 to 0.21) 40 Months • 95.4% letrozole vs 95% placebo Event HR • 0.82 (0.57 to 1.19)	0.25 0.3

ABCSG: Austrian Breast and Colorectal Cancer Study Group; CI: confidence interval; DATA: Different Durations of Adjuvant Anastrozole Therapy; ER: estrogen receptor; HR: hazard ratio; IDEAL: Investigation on the Duration of Extended Adjuvant Letrozole; ITT: intention to treat; NCIC CTG: National Cancer Institute Clinical Trials Group; NS: not significant; NSABP: National Surgical Adjuvant Breast and Bowel Project; PR: progesterone receptor; RR: rate ratio; TAM: tamoxifen.

In addition to the trials published in full-length form, 3 trials 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 to 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 (OS). 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 human epidermal growth factor receptor (*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	21-gene RT-PCR; identifies 3 groups as low, intermediate, and high risk for distant recurrence
EndoPredict®	Sividon Diagnostics (acquired by Myriad in 2016)	12-gene real-time RT-PCR; gene expression molecular score alone (EP) or EP is combined with the clinical parameters of tumor size and number positive lymph nodes (EPclin), resulting in classifications of EP low, EP high, EPclin low, or EPclin high risk for distant recurrence
Breast Cancer Index Prognostic[SM]	Biotheranostics	Combines MGI and the HOXB13:IL17BR Index measured using RT-PCR; identifies 2 groups as low or high risk for distant recurrence
MammaPrint®	Agendia	70-gene DNA microarray; identifies 2 groups as low or high risk for distant recurrence
Prosigna®	NanoString Technologies	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; POR; 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 (ie, luminal A, luminal B, *HER2* type, and basal type). Prosigna was initially offered a molecular subtype test. The BluePrint® 80-gene molecular subtyping assay 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.[22] 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 (eg, 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.[22] Simon also proposed that while "further confirmation in a separate trial of the results gained from a category A prospective trial is always welcome, compelling results from such a trial would be considered definitive and no other validating trial would be required."[22]

Breast Cancer–Specific Outcomes

The main outcome of interest for this review is 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.

Historically, 10-year distant recurrence has been the outcome of interest for assessing prognostic tests used to select women with early-stage breast cancer who can avoid treatment with adjuvant chemotherapy.[23] In 2012, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducted a patient data meta-analysis of 123 trials (N>100,000 women) that compared various chemotherapy regimens with no chemotherapy for early-stage breast cancer.[24] The pooled results showed that women receiving chemotherapy experienced significantly lower rates of distant recurrence compared with women not receiving chemotherapy for up to 5 years; however, during the 5- to 10-year follow-up period, recurrence rates were similar between the 2 groups. This would suggest that any benefit of chemotherapy can be observed with 5 years of follow-up. As a result, BCBSA has revised requirement for duration of follow-up from 10 to 5 years when assessing prognosis in women considering adjuvant chemotherapy.

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.[25,26] 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.[27] 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.[28] About half felt a single day would justify adjuvant chemotherapy. A major difference between the 2 studies was that the chemotherapy regimen in the Duric study 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.[29] 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.[30] 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).[31] There was a wide range of minimally required absolute benefits, with most 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

Age Range, y	Proportion That Would Accept 1% to 10% Benefit	
	Chemotherapy, %	Endocrine, %
40-49	78	78
50-59	88	44
60-69	59	63
≥70	40	46

Adapted from Hamelinck et al (2016).[31]

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory

standards of the Clinical Laboratory Improvement Amendments (CLIA). Oncotype DX®
and other tests listed herein are available under the auspices of CLIA. Laboratories that
offer LDTs must be licensed by CLIA for high-complexity testing. To date, the 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 FDA through
the 510(k) process. In January 2015, MammaPrint® was cleared for marketing by FDA
through the 510(k) process for use in fresh-frozen, paraffin-embedded breast cancer
tissue.

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

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

FDA product code: NYI.

POLICY
A.   The use of Oncotype DX, 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 individuals with
      primary, invasive breast cancer meeting **ALL** of the following characteristics:

      1.   unilateral tumor; **AND**
      2.   hormone receptor-positive (that is, estrogen-receptor [ER]-positive or
            progesterone receptor [PR]-positive); **AND**
      3.   human epidermal growth factor receptor 2 (HER2)-negative; **AND**
      4.   tumor size 0.6 to 1 cm with moderate/poor differentiation or unfavorable
            features OR tumor size larger than 1 cm; **AND**
      5.   node negative (lymph nodes with micrometastases [less than 2 mm in size] are
            considered node negative for this policy statement); **AND**
      6.   who will be treated with adjuvant endocrine therapy, eg, tamoxifen or
            aromatase inhibitors; **AND**
      7.   when the test result will aid the patient in making the decision regarding
            chemotherapy (ie, when chemotherapy is a therapeutic option); **AND**
      8.   when ordered within 6 months following diagnosis, since the value of the test
            for making decisions regarding delayed chemotherapy is unknown.

B.   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 (ie, the test should not be ordered on a preliminary core biopsy).

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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.

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

D.   All other indications for 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 length of treatment with tamoxifen, are considered **experimental / investigational**.

E.   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 (ie, Oncotype DX Breast DCIS Score) to inform treatment planning following excisional surgery is considered **experimental / investigational**.

F.   The use of BluePrint in conjunction with MammaPrint or alone is considered **experimental / investigational**.

RATIONALE

The most recent literature update for all indications was performed through September 4, 2018.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Assays of Genetic Expression on 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 women with breast cancer?

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

Patients
The populations of interest include:
- Women with early-stage node-negative or node-positive invasive breast cancer considering adjuvant chemotherapy;
- Women with DCIS considering radiotherapy; and
- Women 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. For adjuvant chemotherapy, a conventional risk classifier (eg, Adjuvant! Online) estimates recurrence risk by considering criteria such as tumor size, type, grade, and histologic characteristics; hormone receptor status; and lymph node status. No single classifier is considered a criterion standard. Several common criteria have qualitative or subjective components that add variability to risk estimates. A risk classifier tool to guide the use of extended therapy has been developed and validated in 2018 (Clinical Treatment Score post-5 years [CTS5]), but was not available at the time the studies providing evidence in this review were conducted.

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, they 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, they may be able to safely forgo extended endocrine therapy.

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

For patients with DCIS, the assays would be performed following the diagnosis of DCIS, when patients are considering radiotherapy.

For patients with early-stage invasive node-negative breast cancer who are recurrence-free for 5 years, the assays would be performed when patients are considering extended endocrine therapy.

<u>*Setting*</u>
The setting is a laboratory meeting general regulatory standards of the Clinical Laboratory Improvement Amendments.

<u>Technically Reliable</u>
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Early-Stage Node-Negative Invasive Breast Cancer Considering Adjuvant Chemotherapy
<u>Oncotype DX (21-Gene Assay)</u>
<u>*Clinically Valid*</u>
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Low-Risk Threshold (Recurrence Scores ≤10): BCBSA identified 4 studies meeting selection criteria for the low-risk category (see Appendix 1).[32-35] 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.[34] The study by Tang et al (2011)[35] represents the same results as Paik et al (2004),[33] 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),[30] 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).[36] 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.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence: Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

Low-Risk Threshold (Recurrence Scores ≤10): Evidence for clinical validity has shown that patients within the low-risk threshold for Oncotype DX may consider safely forgoing adjuvant chemotherapy with tight precision, and thereby avoid negative effects of the therapy (see Table 5).

Intermediate-Risk Threshold (Recurrence Scores 11-25): Sparano et al (2018) conducted an RCT (TAILORx) to evaluate risk of recurrence in women with midrange scores.[37] Women with intermediate-risk scores were randomized to endocrine therapy (n=3399) or chemoendocrine therapy (n=3312). Women with low-risk scores (≤10) received endocrine therapy (n=1619) and women with high-risk scores (≥26) received chemoendocrine therapy (n=1389). Overall disease-free survival estimates showed that adjuvant endocrine therapy was noninferior to chemoendocrine therapy in women with intermediate-risk scores (see Table 6). However, subgroup analyses by age showed women younger than 50 may benefit from chemotherapy.

Table 5. Ten-Year Distant Recurrence by Oncotype DX Risk Score Group

Study (Source of Patients)	N	Risk Score Group by % Patients in Risk Group			10-Year Distant Recurrence (95% Confidence Interval), %		
		Low	Int	High	Low	Int	High
Paik et al (2004)[33] (TAM arm of NSABP B-14 trial)	668	51	22	27	6.8 (4.0 to 9.6)	14.3 (8.3 to 20.3)	30.5 (23.6 to 37.4)
Paik et al (2006)[34] (TAM arm of NSABP B-20 trial)	227	59	20	21	3.2 (0.1 to 6.3)	9.1 (0.6 to 17.5)	39.5 (25.2 to 53.8)
Tang et al (2011)[35] (TAM arm of NSABP B-14 trial)	668	Clin low/RS low: 32 Clin low/RS int-high: 21 Clin int-high/RS low: 18 Clin int-high/RS int-high: 29			5.6 (2.5 to 9) 12.9 (7 to 19) 8.9 (4 to 14) 30.7 (24 to 38)		
Buus et al (2016)[32] (ATAC trial)	680	64	27	10	5.3 (3.5 to 8.2)	14.3 (9.8 to 20.6)	25.1 (15.8 to 38.3)
Sestak et al (2018)[38] (ATAC trial)	591	374	156	61	5.9 (3.8 to 9.1)	16.7 (11.5 to 24.0)	27.2 (17.3 to 41.2)

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

Table 6. Survival and Distant Recurrence Estimates by Oncotype DX RS[37]

RS	Therapy	DFS Rate (SD)		Free From DR Rate (SD)		OS Rate (SD)	
		5 Year	9 Year	5 Year	9 Year	5 Year	9 Year
Low	Endocrine	94.0 (0.6)	84.0 (1.3)	99.3 (0.2)	96.8 (0.7)	98.0 (0.4)	93.7 (0.8
Intermediate	Endocrine	92.8 (0.5)	83.3 (0.9)	98.0 (0.3)	94.5 (0.5)	98.0 (0.2)	93.9 (0.5)
Intermediate	Chemoendocrine	93.1 (0.5)	84.3 (0.8)	98.2 (0.2)	95.0 (0.5)	98.1 (0.2)	93.8 (0.5)
High	Chemoendocrine	87.6 (1.0)	75.7 (2.2)	93.0 (0.8)	86.8 (1.7)	95.9 (0.6)	89.3 (1.4)

DFS: disease-free survival; DR: distant recurrence; Int: intermediate; OS: overall survival; RS: Recurrence Score; SD: standard deviation.

Section Summary: Oncotype DX (21-Gene Assay)
Multiple studies using archived samples of previously conducted 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%. These low absolute risks would translate to small absolute benefit from adjuvant chemotherapy. In these studies, over half of patients were classified as low risk. The prospective study by Sparano et al (2015), 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.

One RCT randomizing women with intermediate-risk scores to endocrine therapy alone or chemoendocrine therapy reported that endocrine therapy alone was noninferior to chemoendocrine therapy in disease-free survival, distant recurrence, and overall survival.[37]

EndoPredict
Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

BCBSA identified 2 studies with 4 sets of findings that met selection criteria (see Table 7). The study by Filipits et al (2011) assessed patients from 2 previously conducted clinical trials.[39] BCBSA 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) and Sestak et al (2018) studied patients from the ATAC trial, which evaluated the efficacy and safety of anastrozole vs tamoxifen in postmenopausal women with localized breast cancer.[32,38] 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 supplemental 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 4 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 CI 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.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence: Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.
No decision-impact studies were identified that provide clinical outcomes such as survival or recurrence.

Chain of Evidence: Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. 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.

Table 7. Ten-Year Distance Recurrence by EndoPredict Risk Group

Study (Source of Patients)	N	Risk Score Group by % Patients in Risk Group				10-Year Distant Recurrence (95% Confidence Interval), %			
		EP Low	EP High	EPclin Low	EPclin High	EP Low	EP High	EPclin Low	EPclin High
Filipits et al (2011)[39,a] (ABCSG-6 trial)	378	51	49	55	45	8 (3 to 13)	22 (15 to 29)	4 (1 to 8)	28 (20 to 36)
Filipits et al (2011)[39,a] (ABCSG-8 trial)	1324	48	52	65	35	6 (2 to 9)	15 (11 to 20)	4 (2 to 5)	22 (15 to 29)
Buus et al (2016)[32] (ATAC trial)	680	43	57	73	27	3.0 (2 to 6)	14.6 (11 to 19)	5.9 (4 to 9)	20.0 (15 to 27)
Sestak et al (2018)[38] (ATAC trial)	591	NR	NR	429	162	NR	NR	7 (4 to 10)	22 (16 to 30)

ABCSG: Austrian Breast and Colorectal Cancer Study Group; ATAC: Arimidex, Tamoxifen, Alone or in Combination; EP: expression profile score; EPclin: EndoPredict score; NR: not reported.
[a] ABCSG-6 and ABCSG-8 studies included a combined 32% node-positive patients.

Section Summary: EndoPredict
Several 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.

Breast Cancer Index

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

BCBSA identified 4 sets of findings using samples from 2 RCTs and a registry for the BCI that met selection criteria (see Table 8).[40,41] Some *HER2*-positive patients were included in both studies, but the number was not provided. Sgroi et al (2013)[40] and Sestak et al (2018)[38] analyzed patients receiving anastrozole or tamoxifen in the ATAC trial. This trial constitutes a Simon category B study. Two versions of the BCI score were generated in the study: (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.[41] Patients from the registry were only included if tissue samples were available.

In all sets of findings, the BCI classified more than half of the patients as low risk, and these patients had low risk of disease recurrence at 10 years. The Sgroi and Sestak studies reported 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 study, patients in BCI low-risk categories also showed a low risk of distant disease recurrence, with CIs not exceeding 10%.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence: Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No decision-impact studies were identified that report clinical outcomes such as survival or recurrence.

Chain of Evidence: Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. Evidence for clinical validity has shown that the BCI is able to identify women who can safely forgo adjuvant chemotherapy with tight precision, and thereby avoid negative effects of the therapy.

Table 8. Ten-Year Distance Recurrence by BCI Risk Group

Study (Source of Patients)	N	Risk Score Group by % Patients in Risk Group			10-Year Distant Recurrence (95% Confidence Interval), %		
		BCI Low	BCI Int	BCI High	BCI Low	BCI Int	BCI High
Zhang et al (2013)[41] (multicenter registry)	358	55	22	23	6.6 (2.9 to 10)	23.3 (12.3 to 33)	35.8 (24.5 to 45.5)
Zhang et al (2013)[41] (Stockholm trial)	317	64	20	16	4.8 (1.7 to 7.8)	11.7 (3.1 to 19.5)	21.1 (8.5 to 32.0)
		BCI-C Low	BCI-C Int	BCI-C High	BCI-C Low	BCI-C Int	BCI-C High

Study (Source of Patients)	N	Risk Score Group by % Patients in Risk Group			10-Year Distant Recurrence (95% Confidence Interval), %		
Sgroi et al (2013)[40] (ATAC trial)	665	58	25	17	6.8 (4.4 to 10)	17.3 (12.0 to 24.7)	22.2 (15.3 to 31.5)
		59	25	16	4.8 (3.0 to 7.6)	18.3 (12.7 to 25.8)	29.0 (21.1 to 39.1)
Sestak et al (2018)[38] (ATAC trial)	591	365	143	83	3.9 (2.3 to 6.7)	19.3 (13.3 to 27.6)	27.3 (18.7 to 38.8)

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.

Section Summary: Breast Cancer Index

Four sets of findings for the BCI 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.

MammaPrint (70-Gene Signature)
Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

BCBSA identified 2 studies using MammaPrint that met selection criteria (see Table 9). Several studies could not be included due to mixed populations, including node-positive patients, mixed node-positive, 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.[42] The study sample was derived from 3 separate cohorts in cancer registry studies (Simon category C). For this evidence review, BCBSA presents 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.[43] 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 9. Ten- and 20-Year Follow-up Results by MammaPrint Risk Group

Study (Source of Patients)	N	MP Risk Score Group, n (%)	10-Year DMFS (95% CI), %	20-Year BCSS (95% CI), %
Van 't Veer et al (2017)[43,a]	538	Low risk, with tamoxifen: 199 (37) Low risk, without tamoxifen: 172 (32) High risk, with tamoxifen: 82 (15) High risk, without tamoxifen: 85 (16)	93 (88 to 96) 83 (76 to 88) 85 (75 to 91) 70 (58 to 79)	90 (84 to 94) 80 (72 to 86) 83 (72 to 90) 65 (53 to 75)
		Clinical Risk Score Group and MP Risk Score Group, n (%)	10-Year Distant Recurrence (95% CI), %	
Bueno-de-Mesquita et al (2011)[42] (3 combined cohorts)	139	Clin low/low MP low: 24 Clin low/low MP high: 10 Clin discordant MP low: 22 Clin discordant MP high: 9 Clin high/high MP low: 9 Clin high/high MP high: 26	3 (0 to 9) 34 (9 to 59) 11 (0 to 22) 31 (6 to 56) 23 (0 to 46) 47 (31 to 63)	

BCSS: breast cancer–specific survival; CI: confidence interval; Clin: clinical; DMFS: distant metastases-free survival; MP: MammaPrint.
[a] Confidence intervals provided by the manufacturer in October 2017.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence: Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

The MINDACT trial (Cardoso et al [2016]) is a prospectively designed trial evaluating MammaPrint, with additional randomized components (see Table 10).[44] 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 to no chemotherapy. Women at high risk with both methods received chemotherapy.

Although parts of the study are an RCT, the end point for this particular analysis was the distant recurrence rate among patients with high-risk clinical and low-risk genetic profile who did not receive chemotherapy. 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 (HR) 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 CIs were wide and thus less informative regarding whether chemotherapy is or is not beneficial in these patient groups. In the main study, the 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 10. MINDACT Trial 5-Year Distant Recurrence for the Node-Negative, Estrogen Receptor–Positive, or *HER2*-Negative Subgroup

Study (Trial)	N	Risk Score Group by % Patients in Risk Group	5-Year Distant Recurrence (95% Confidence Interval), %
Cardoso et al (2016)[44] (MINDACT trial)	4225	Clin low/MP low: 58	2.4 (1.8 to 3.1)
		Clin low/MP high: 11	6.1 (3.9 to 9.4)
		Clin high/MP low: 17	4.5 (2.4 to 8.4)
		Clin high/MP high: 14[a]	9.1 (6.8 to 12)

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.
[a] All clin high/MP high subjects received chemotherapy.

Chain of Evidence: Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. Evidence for clinical validity has shown that the MammaPrint is able to identify women who can safely forgo adjuvant chemotherapy with tight precision, and thereby avoid negative effects of the therapy.

Section Summary: MammaPrint (70-Gene Signature)
Evidence for the use of MammaPrint to identify low-risk women considering adjuvant chemotherapy consists of 1 category A study (Cardoso et al [2016]), 1 category B study (van 't Veer et al [2017]), and 1 category C study (Bueno-de-Mesquita et al [2011]). The Simon category C study and Simon category B study 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 rates, in both low- and high-risk groups. However, the 10-year DMFS estimates for those identified by MammaPrint as low risk, include values higher than the prespecified 10% threshold to safely forgo adjuvant chemotherapy. The Simon category A study of MammaPrint has currently provided 5-year distant recurrence outcomes, which have shown that patients identified by MammaPrint as low risk (both clinically low risk and clinically high risk) had low distant recurrence rates, within the 10% threshold. Evidence is sufficient based on the category A prospective trial.

Prosigna
Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Three studies using samples from 2 RCTs that met selection criteria were identified (both studies are classed as Simon category B).[45,46] 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 11 are based on visual estimates of the graphic results; CIs are not available.).[45] 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.

Clinically Useful: A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence: Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No decision-impact studies were identified that report clinical outcomes such as survival or recurrence.

Chain of Evidence: Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. Evidence for clinical validity has shown that Prosigna is able to identify women who can safely forgo adjuvant chemotherapy with tight precision, and thereby avoid negative effects of the therapy.

Table 11. Ten-Year Distant Recurrence by Prosigna Recurrence Score Group

Study (Trial)	N	Risk Score Group (% Patients in Risk Group)			10-Year Distant Recurrence (95% Confidence Interval), %		
		Low	Int	High	Low	Int	High
Gnant et al (2014)[46] (ABCSG-8 trial)	1047	47	32	22	3.4 (2.1 to 5.6)	9.6 (6.7 to 13.7)	15.7 (11.4 to 21.6)
Dowsett et al (2013)[45] (ATAC trial)	739	59	33	8	4.8 (NR)	13.8 (NR)	30.2 (NR)
Sestak et al (2018)[38] (ATAC trial)	591	318	178	95	3.0 (1.6 to 5.8)	14.1 (9.4 to 20.8)	32.4 (23.4 to 43.8)

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

Section Summary: Prosigna

Three category Simon B studies using samples from 2 different populations 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 variations in the tests used in these different studies.

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

Table 12 summarizes the studies that met selection criteria (see Appendix 1), which were 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,[47,48] Prosigna ROR (risk of recurrence)[49] in 1 study, and EndoPredict in 2 studies. Albain et al (2010) also explored a possible role for Oncotype DX in predicting chemotherapy benefit.[47] BCBSA also discusses results from the MINDACT trial, a prospectively designed trial evaluating MammaPrint. Table 12 displays the characteristics of patients assessed across the prospective-retrospective analyses. Almost all cancers were estrogen receptor–positive and *HER2*-negative, most patients had 3 or fewer positive lymph nodes, and all women were postmenopausal.

Table 12. Characteristics of Patients Included in Node-Positive Prospective-Retrospective Studies

Study	N	ER+	HER2 +	Tumor Size			Nodes		Adjuvant Chemo	Trial/Study
				≤2 cm	2-5 cm	>5 cm	1-3	≥4		
Oncotype DX										
Albain (2010)[47,a]	148	145 (98)	13 (9)	46 (31)	94 (64)	8 (5)	94 (64)	54 (36)	0 (0)	SWOG-8814
Albain (2010)[47,b]	219	210 (96)	30 (14)	74 (34)	136 (62)	9 (4)	133 (61)	86 (39)	219 (100)	
Dowsett (2010)[48]	306	306 (100)	NR for node-positive patients				243 (79)	63 (21)	0 (0)	TransATAC
Sestak (2018)[38]	183	183 (100)	0 (0)	NR			183 (100)	0	0 (0)	TransATAC
EndoPredict										
Filipits (2011)[39]	537	537 (100)	0 (0)	NR for node-positive patients			454 (85)	83 (15)	0 (0)	ABCSG-6, ABCSG-8
Buus (2016)[32]	248	248 (100)	0 (0)	NR for node-positive patients			198 (80)	50 (20)	0 (0)	TransATAC
Sestak (2018)[38]	183	183 (100)	0 (0)	NR			183 (100)	0	0 (0)	TransATAC
Prosigna										
Gnant (2015)[49]	543		28 (5)	314 (58)			229 (42)	0 (0)	543 (100)	ABCSG-8
Sestak (2018)[38]	183	183 (100)	0 (0)	NR			183 (100)	0	0 (0)	TransATAC
Breast Cancer Index										
Sestak (2018)[38]	183	183 (100)	0 (0)	NR			183 (100)	0	0 (0)	TransATAC

All values are n (%) unless otherwise noted.
ABCSG: Austrian Breast and Colorectal Cancer Study Group; ATAC: Arimidex, Tamoxifen, Alone or in Combination; chemo: chemotherapy; ER: estrogen receptor; *HER2*: human epidermal growth factor receptor 2; NR: not reported.

[a] Tamoxifen.
[b] Cyclophosphamide, doxorubicin, and fluorouracil chemotherapy followed by tamoxifen.

Table 13 displays 10-year event rates 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%.[49] None of the studies reported the ability of tests to reclassify after assigning risk based on clinical predictors.

Table 13. Ten-Year Results by Risk Categories in Node-Positive Breast Cancer Studies

Study	Total N	n	Low Risk	n	Intermediate Risk	n	High Risk
Oncotype DX		n	DFS % (95% CI)	n	DFS % (95% CI)	n	DFS % (95% CI)
Albain (2010)[47,a]	148	55	60 (NR)	46	49 (NR)	47	43 (NR)
		n	OS % (95% CI)	n	OS % (95% CI)	n	OS % (95% CI)
Albain (2010)[47,b]	148	55	77 (NR)	46	68 (NR)	47	51 (NR)
Dowsett (2010)[48]	296	150	74 (NR)	94	69 (NR)	52	54 (NR)
		n	DR % (95% CI)	n	DR % (95% CI)	n	DR % (95% CI)
Dowsett (2010)[48, a]	296	150	17 (12 to 24)	94	28 (20 to 49)	52	49 (35 to 54)
Sestak (2018)[38]	183	105	19 (13 to 29)	58	29 (19 to 43)	20	38 (20 to 64)
EndoPredict							
Filipits (2011)[39] (EP)	537	240	15 (NR)	NA	NA	297	27 (NR)
Buus (2016)[32, a] (EP)	248	94	21 (14 to 32)	NA	NA	154	36 (29 to 45)
Buus (2016)[32, a] (EPclin)	248	47	5 (1 to 19)	NA	NA	201	37 (30 to 45)
Sestak (2018)[38] (EPclin)	183	43	5 (1 to 21)	NA	NA	140	30 (23 to 39)
Prosigna							
Gnant (2015)[49, b] (total)	331	132	7 (2 to 13)	106	15 (9 to 25)	93	25 (17 to 36)
Gnant (2015)[49, b] (≥2 nodes)	212			83[c]	12 (7 to 23)	129	34 (25 to 44)
Sestak (2018)[38]	183	15	0	58	21 (12 to 34)	110	31 (22 to 41)
Breast Cancer Index							
Sestak (2018)[38]	183	95	15 (9 to 25)	60	32 (21 to 47)	28	41 (24 to 64)

CI: confidence interval; DFS: disease-free survival; DR: distant recurrence; EP: expression profile score; EPclin: EndoPredict score ; NA: not applicable; 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)
Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

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.[47] 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 an *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 14). While the HRs 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 14. Hazard Ratios for Chemotherapy Benefit of Sequential CAF-T vs Tamoxifen Alone by Oncotype DX RS

Variables	Overall Survival, HR (95% CI)		Disease-Free Survival, HR (95% CI)	
	10 Years	10 Years	≤5 Years	≥5 Years
Parent trial	0.78 (0.63 to 0.97)	0.69 (0.56 to 0.84)	0.68 (0.53 to 0.86)	0.72 (0.51 to 1.00)
RS sample[a]	0.77 (0.52 to 1.14)	0.72 (0.51 to 1.00)	0.79 (0.53 to 0.86)	0.63 (0.39 to 1.04)
Low RS			1.34 (0.47 to 3.82)	0.88 (0.38 to 1.92)
Intermediate RS			0.95 (0.43 to 2.14)	0.52 (0.20 to 1.52)
High RS			0.59 (0.32 to 1.11)	0.60 (0.22 to 1.62)

Adapted from Albain et al (2010).[47]
CAF-T: cyclophosphamide, doxorubicin, and fluorouracil chemotherapy followed by tamoxifen; CI: confidence interval; HR: hazard ratio; RS: Recurrence Score.
[a] Adjusted for number of positive nodes.

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 (ie, 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).[48] 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)[27,30] raises a question whether in practice the RS offers sufficient prognostic information to inform decisions.

Nitz et al (2017) conducted a phase 3 PlanB trial with a mixed population of women with node-negative and node-positive breast cancer.[50] 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.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence: Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No decision-impact studies were identified that report clinical outcomes such as survival or recurrence.

Chain of Evidence: Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. 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,[51,52] convincing evidence that decisions based on test results will improve outcomes is lacking, and guidelines do not offer support.[53] 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
Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Buus et al (2016) reported on the prognostic value of EndoPredict among node-positive patients from ATAC in the article supplement (Simon category B).[32] 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 rates 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 rates 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.

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).[39] 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 distance 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 distance 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.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence: Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No decision-impact studies were identified that report clinical outcomes such as survival or recurrence.

Chain of Evidence: Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. 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 estimate 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)
Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Mook et al (2009) evaluated the prognostic value of MammaPrint in patients with node-positive breast cancer.[54] 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.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence: Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

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.[44] 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).

Chain of Evidence: Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

One Simon category C study provided evidence for clinical validity. The category A study, providing evidence for clinical utility, provided distant recurrence rates by chemotherapy group, but did not provide distant recurrence rates by low risk and high risk categories.

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, however, distant recurrence rates for patients categorized as low risk and high risk were not provided.

Prosigna
Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

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.[49] 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.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence: Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the RCTs.

No decision-impact studies were identified that provide clinical outcomes such as survival or recurrence.

Chain of Evidence: Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. 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 (Gnant et al [2015]) 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 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 RT

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.

Oncotype DX Breast DCIS Score
Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Rakovitch et al (2018)[55] combined the populations from the 2 studies described below (Solin et al [2013][56] and Rakovitch et al [2015][57]) and calculated 10-year local recurrence rates by DCIS category (low, intermediate, and high), age, tumor size, and year of diagnosis (see Table 15). This is a Simon category C study. Ten-year recurrence risks by DCIS category, age, and tumor size, are listed in Table 16.

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 (see Table 15).[57] 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. The Oncotype DX Breast DCIS Score was significantly associated with local recurrence outcomes (HR=2.15; 95% CI, 1.43 to 3.22). Ten-year recurrence risks by DCIS category are listed in Table 16.

In a retrospective analysis of data and samples from patients in the prospective Eastern Cooperative Oncology Group E5194 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 (see Table 15).[56] 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. Ten-year recurrence risks by DCIS category are listed in Table 16. Whether women are better categorized as to their local recurrence risk by Oncotype DX Breast DCIS Score compared with standard clinical indicators of risk was not addressed.

Table 15. Characteristics of Retrospective Studies Evaluating the Oncotype DX DCIS Score

Study	Country	Study Population	Design	N	Median FU, y
Rakovitch et al (2018)[55]	Canada	Combined patients from ECOG E5194 and Ontario DCIS cohort	Retrospective	773	11.5
Rakovitch et al (2015)[57]	Canada	Patients with DCIS who had breast-conserving surgery without RT, from Ontario DCIS cohort	Retrospective	571	9.6
Solin et al (2013)[56]	Canada	Patients with DCIS who had breast-conserving surgery without RT, from ECOG E5194 study	Retrospective	327	8.8

DCIS: ductal carcinoma in situ; ECOG: Eastern Oncology Cooperative Group; FU: follow-up; RT: radiotherapy.

Table 16. Ten-Year Local Recurrence by Oncotype DCIS Score Groups

Study	N	Patients by Risk Score Group,			Events	10-Year Recurrence Rates (95% Confidence Interval), %		
		Low	Int	High		Low	Int	High
Rakovitch et al (2018)[55]								
Overall local recurrence[a]	773	70.3	16.2	13.5	118	NR	NR	NR
Tumor ≤1 cm, age ≥50	NR	NR	NR	NR	NR	7.2 (5.3 to 10.0)	11.3 (10.2 to 12.7)	14.6 (12.9 to 23.1)
Tumor ≤1 cm, age <50	NR	NR	NR	NR	NR	10.2 (7.4 to 13.9)	15.8 (14.1 to 17.4)	19.6 (17.7 to 30.7)
Tumor 1.1-2.5 cm, age ≥50	NR	NR	NR	NR	NR	10.1 (7.3 to 12.6)	13.9 (12.8 to 15.6)	19.5 (15.8 to 28.7)
Tumor 1.1-2.5 cm, age ≥50	NR	NR	NR	NR	NR	14.5 (10.1 to 17.2)	18.9 (17.4 to 21.1)	23.2 (21.4 to 37.2)
Invasive BC recurrence	773	70.3	16.2	13.5	65	NR	NR	NR
Tumor ≤2.5 cm	NR	NR	NR	NR	NR	5.3 (3.6 to 7.4)	8.5 (7.5 to 9.8)	12.1 (10.0 to 20.5)
Tumor >2.5 cm	NR	NR	NR	NR	NR	11.6 (7.7 to 15.5)	17.1 (15.8 to 20.3)	26.2 (20.6 to 40.0)
Rakovitch et al (2015)[57]								
Overall local recurrence[a]	571	62.2	16.6	21.2	100	12.7 (9.5 to 16.9)	33.0 (23.6 to 44.8)	27.8 (20.0 to 37.8)
DCIS recurrence	571	62.2	16.6	21.2	43	5.4 (3.4 to 8.6)	14.1 (8.2 to 23.6)	13.7 (8.5 to 21.8)
Invasive BC recurrence	571	62.2	16.6	21.2	57	8.0 (5.5 to 11.5)	20.9 (12.9 to 32.9)	15.5 (9.3 to 25.1)
Solin et al (2013)[56]								
Overall local recurrence[a]	327	70.3	16.2	13.5	46	10.6 (6.9 to 16.2)	26.7 (16.2 to 41.9)	25.9 (14.8 to 43.1)
DCIS recurrence	327	70.3	16.2	13.5	26	7.2 (4.1 to 12.3)	16.1 (8.3 to 29.8)	7.9 (2.6 to 22.6)
Invasive BC recurrence	327	70.3	16.2	13.5	20	3.7 (1.8 to 7.7)	12.3 (5.1 to 27.8)	19.2 (9.5 to 36.4)

BC: breast cancer; DCIS: ductal carcinoma in situ; Int: intermediate; NR: not reported.
[a] Local recurrence of DCIS and invasive carcinoma combined.

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The evidence gaps stated in Tables 17 and 18 are those notable in the current review; this is not a comprehensive gaps assessment.

Table 17. Relevance Gaps

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Rakovitch et al (2018)[55]			3. No comparator (standard of care is clinical risk indicators)		
Rakovitch et al (2015)[57]			3. No comparator (standard of care is clinical risk indicators)		
Solin et al (2013)[56]			3. No comparator (standard of care is clinical risk indicators)		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 18. Study Design and Conduct Gaps

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Rakovitch et al (2018)[55]	2. Convenience sample of women from another study and registry combined					
Rakovitch et al (2015)[57]	2. Convenience sample of women from registry					
Solin et al (2013)[56]	2. Convenience sample of women from another study					

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence: Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No decision-impact studies were identified that provide clinical outcomes such as survival or recurrence.

Chain of Evidence: Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. One of Simon category B and 2 Simon category C studies provided evidence for clinical validity. The category B study showed an invasive breast cancer recurrence rate under the 10% threshold. The 2 Simon category C studies did not show distant recurrence rates under the threshold, except for 2 small subgroups.

Section Summary: Oncotype DX Breast DCIS Score
Evidence consists of 1 Simon category B study and 2 Simon category C studies. 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, as most of the point-estimates and CIs included the threshold of 10%, except for estimates for 2 subgroups: (1) patients ages 50 and older with tumors 1 centimeter or less in size and (2) patients with tumors 2.5 centimeter or less in size. Conclusions are also limited because there are no comparison recurrence estimates for women based on standard of care (risk predictions based on clinical algorithms).

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

Extended Adjuvant Endocrine Therapy Beyond 5 Years
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 absolute benefit and certainty of benefit from extended endocrine therapy, (2) whether a test accurately discriminates good from poor outcomes (ie, prognostic value for recurrences) at those thresholds, and (3) whether the test provides incremental improvement over clinical risk prediction algorithms or tools.

Multiple RCTs have demonstrated improvements in overall and BCSS outcomes with 5 to 10 years of tamoxifen for estrogen receptor–positive tumors. Results from trials using aromatase inhibitors following 5 years of endocrine therapy have reported inconsistent benefits in BCSS and duration of aromatase inhibitor use is uncertain (see Table 2). In addition, 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.[58] 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.

Currently, physicians and patients use clinicopathogic parameters such as tumor size and nodal status to estimate risk of breast cancer recurrence while deciding on extended endocrine therapy. A clinical tool was developed and validated in 2018 (CTS5).[59] This tool did not exist when the studies providing evidence for extended therapy were conducted. The tool is simple to use and incorporates clinical parameters (tumor size, tumor grade, age, and number of nodes) that physicians and patients currently use when considering extended endocrine therapy. CTS5

identified 42% of women with less than 1% risk of distant recurrence, who may be advised to safely forgo extended endocrine therapy. Distant recurrence rates using the CTS5 have been added to Table 19, to compare with distant recurrence rates calculated using gene expression profiling tests.

Table 19 summarizes the characteristics of studies that met selection criteria (see Appendix 1) that examined the prognostic value of a gene expression profiling test for late distant recurrences after 5 years of endocrine therapy.[40,41,60-64,38] All 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. The study by Zhang et al (2013)[41] examining prognosis and an additional nested case-control study (Sgroi et al [2013])[65] 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)[41] included only postmenopausal women. Samples from several studies were used multiple times in analyses for the different molecular assays. Table 20 summarizes distant recurrence rates. Some studies provided results other than distant recurrence rates; those results appear in Tables 21, 22, and 23.

Table 19. Characteristics of Patients in Extended Endocrine Therapy Studies of Prognosis or Predicting Treatment Benefit

Study	N	Tumor Size, n (%)		Nodes, n (%)			Adjuvant Chemo, n (%)	Trial
		≤2 cm	>2 cm	None	1-3	≥4		
Oncotype DX								
Sestak (2013)[63]	940			683 (73)	257 (27)		0 (0)	TransATAC
Sestak (2018)[38]	689			535 (78)	154 (22)		0 (0)	TransATAC
EndoPredict								
Dubsky (2013)[60,a]	1702	1136 (67)	563 (33)	1165 (68)	454 (27)	83 (5)	0 (0)	ABCSG-6, ABCSG-8
Sestak (2018)[38]	689			535 (78)	154 (22)		0 (0)	TransATAC
Breast Cancer Index								
Zhang (2013)[41]	285	259 (82)	55 (17)	285 (100)	0 (0)	0 (0)	0 (0)	Stockholm Trial TAM-treated
	358	237 (66)	121 (34)	358 (100)	0 (0)	0 (0)	115 (32)	2-institution cohort
Sgroi (2013)[40]	597	442 (74)	155 (26)	597 (100)	0 (0)	0 (0)	0 (0)	TransATAC
Sgroi (2013)[65]	249	110 (44)	139 (56)	94 (38)	146 (59)		148 (59)	Nested case-control in MA.17
Sestak (2018)[38]	689			535 (78)	154 (22)		0 (0)	TransATAC
MammaPrint								
Esserman (2017)[64]	652	499 (77)	145 (22)	652 (100)	0 (0)	0 (0)	0 (0)	Stockholm Trial TAM-treated
Prosigna								
Filipits (2014)[61]	1246	NR (see below)		919 (74)	327 (26)		0 (0)	ABCSG-8
Sestak (2013)[63]	940			683 (73)	257 (27)		0 (0)	TransATAC
Sestak (2015),[62] all patients	862	587 (68)	275 (32)	647 (75)	180 (21)	35 (4)	0 (0)	TransATAC
Sestak (2015),[62] node-negative	1275	938 (74)	337 (26)	933 (73)	307 (24)	35 (3)	0 (0)	ABCSG-8
Sestak (2018)[38]	689			535 (78)	154 (22)		0 (0)	TransATAC
CTS5								
Dowsett (2018)[59]	6711	4378	2333	4090	1944	677	1627 (24.2)	BIG 1-98

ABCSG: Austrian Breast and Colorectal Cancer Study Group; Chemo: chemotherapy; CTS5: Clinical Treatment Score – 5 years; NR: not reported; TAM: tamoxifen; TransATAC: translational substudy of the Arimidex, Tamoxifen, Alone or in Combination.
[a] Sample size and characteristics represent patients at enrollment for Dubsky et al (2013).

Table 20. Distant Recurrence Rates for Extended Endocrine Therapy Studies

Study			Low Risk		Intermediate Risk		High Risk	
	N	Years	n	DR (95% CI), %	n	DR (95% CI), %	n	DR (95% CI), %
Oncotype DX								
Sestak (2013)[63]	940	5-10	NR	7.6 (NR)	NR	NR	NR	17.6 (NR)
Sestak (2018)[38]	535	5-10	351	4.8 (2.9 to 7.9)	134	9.6 (5.6 to 16.3)	50	16.1 (8.0 to 30.8)
EndoPredict								
Dubsky (2013)[60,a] (EP)	998	5-10	503	3.7 (0.9 to 6.5)		NA	495	9.0 (NR)
Dubsky (2013)[60,a] (EPclin)	998	5-10	642	1.8 (0.1 to 3.5)		NA	356	13.0 (NR)
Sestak (2018)[38] (EPclin)	535	5-10	393	4.3 (2.6 to 7.1)		NA	142	14.6 (9.6 to 22.0)
Breast Cancer Index								
Zhang (2013)[41] (Stockholm TAM)	285	5-10	184	2.8 (0.3 to 5.2)	58	7.2 (0.1 to 13.8)	43	10.1 (0.2 to 19.1)
Zhang (2013)[41] (cohort study)	312	5-10	181	2.5 (0.0 to 5.0)	70	16.9 (6.5 to 26.2)	61	15.0 (5.5 to 23.6)
Sgroi (2013)[40]	597	5-10	366	3.5 (2.0 to 6.1)	146	13.4 (8.5 to 20.5)	84	13.0 (7.4 to 23.4)
Sestak (2018)[38]	535	5-10	340	2.6 (1.3 to 5.0)	126	14.4 (9.0 to 22.6)	69	15.9 (8.9 to 27.6)
Prosigna								
Filipits (2014)[61]	1246	5-15	460	2.4 (1.1 to 5.3)	416	9.1 (5.8 to 14.1)	370	17.6 (12.9 to 25.2)
Sestak (2013)[63]	940	5-10	NR	4.1 (NR)	NR	NR	NR	NR
Sestak (2015),[62] all patients	2137	5-10	1183	2.4 (1.6 to 3.5)	538	8.3 (6.1 to 11.2)	416	16.8 (13.1 to 20.9)
Sestak (2015),[62] node-negative	1580	5-10	963	2.0 (1.3 to 3.2)	344	9.0 (6.3 to 13.0)	122	11.5 (6.8 to 19.0)
Sestak (2018)[38]	535	5-10	292	1.4 (0.52 to 3.8)	165	10.0 (6.0 to 16.5)	78	23.2 (14.9 to 35.2)
Clinical Treatment Score 5								
Dowsett (2018)[59]	6714	5-10	2861	3.6 (2.7 to 4.9)	2136	6.9 (5.6 to 8.5)	1714	17.3 (14.8-20.1)
MammaPrint			BCSS % (95% CI)		BCSS % (95% CI)			
Esserman (2017)[64]			Low Risk		High Risk			
	652	10	377	90 (87 to 93)	275	81 (74 to 86)		
		20	377	85 (80 to 89)	275	74 (66 to 80)		
			Ultralow Risk		Low Excluding Ultralow			
		10	98	99 (92 to 100)	279	88 (83 to 91)		
		20	98	95 (86 to 99)	279	82 (76 to 86)		

BCSS: breast cancer-specific survival; CI: confidence interval; DR: distant recurrence; EP: expression profile; EPclin: EndoPredict with clinical factors; NA: not applicable; NR: not reported.
[a] Sample size and characteristics represent patients at enrollment for Dubsky et al (2013).

Oncotype DX (21-Gene Assay)
Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Sestak et al (2013) (previously discussed with the TransATAC study) displayed late distant recurrences for risk categories of Oncotype DX in a Kaplan-Meier curve without CIs.[63] 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.

Sestak et al (2018) reanalyzed 535 TransATAC samples and reported a 5- to 10-year distant recurrence rate of 4.8% (95% CI, 2.9% to 7.9%) for those classified as low risk by Oncotype DX (n=351).[38]

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence: Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No decision-impact studies were identified that report clinical outcomes such as survival or recurrence.

Chain of Evidence: Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. While 1 study provided evidence for clinical validity, no studies comparing genetic test classifications with clinical risk prediction tools were identified. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported.

EndoPredict
Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

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).[60] 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 20). 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). When the EPclin score was separated into the clinical component and molecular component, the molecular information added significantly to the clinical score (p<0.001) in prognostic information.

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.

Sestak et al (2018) analyzed 535 TransATAC samples and reported a 5- to 10-year distant recurrence rate of 4.3% (95% CI, 2.6% to 7.1%) for those classified as low risk by EPclin (n=393).[38]

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence: Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No decision-impact studies were identified that report clinical outcomes such as survival or recurrence.

Chain of Evidence: Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. Two studies provided evidence for clinical validity, showing that EPclin scores adequately predicted the risk of distant recurrence, which would allow for the identification of women who can safely forgo extended endocrine therapy. However, the ability of the test to reclassify patients assessed with a clinical prediction tool was not reported.

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.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Incorporating the BCI as a continuous variable, Zhang et al (2013) developed an "optimized model" to predict early and late distant recurrences.[41] Patient samples from 2 studies were used: 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 19). 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 21). 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.[40] 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 al[41]), 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)[66] 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 (2013). The Stockholm trial had 237 patients, and the U.S. medical center cohort contributed 210 patients who 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 21 lists the 5- to 15-year distant recurrence-free survival rates (as categorized by BCI risk) for the 2 trial populations.

Table 21. Five to 15-Year DRFS by Breast Cancer Index Risk Stratification After 5 Years of Endocrine Therapy

Study	Population	N	Low Risk, % (95% CI)	High Risk, % (95% CI)
Schroeder et al (2016)[66]	Stockholm T1N0 total	237	95.4 (92.1 to 98.8)	86.7 (78.9 to 95.3)
	Stockholm T1N0 HER2-negative	225	95.2 (91.9 to 98.8)	86.9 (78.8 to 95.9)
	Stockholm T1N0 HER2-negative, G1 & G2	204	95.7 (92.5 to 99.1)	90.4 (82.8 to 98.8)
	Multi-institutional T1N0 total	210	98.4 (96.3 to 100)	89.6 (82.4 to 97.4)
	Multi-institutional T1N0 HER2-negative	190	98.4 (96.1 to 100)	87.5 (79.1 to 96.9)
	Multi-institutional T1N0 HER2-negative, G1 & G2	173	98.2 (95.8 to 100)	87.6 (78.5 to 97.7)

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

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence: Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No decision-impact studies were identified that report clinical outcomes such as survival or recurrence.

Chain of Evidence: Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. 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. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported.

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.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

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 who had hormone receptor–positive cancers.[65] 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 (locoregional 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 22).

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 22).[41]

Table 22. Predictive Effect of the H/I Index in the BCI for Extended Endocrine Therapy Benefit

Study	N	Comparators	Low Risk		High Risk		Note
			HR (95% CI)	ARR	HR (95% CI)	ARR	
Sgroi et al (2013)[65]	249	Letrozole vs placebo	0.58 (0.25 to 1.36)	4%	0.33 (0.15 to 0.73)	16.5%	Nested matched CC study; 83 recurrences in 166 controls; 5-y ARRs reported
Zhang et al (2013)[41]	600	Tamoxifen vs placebo	0.67 (0.36 to 1.24)	4.9%	0.35 (0.19 to 0.65)	19.6%	Stockholm trial, 15-y results

ARR: absolute risk reduction; BCI: Breast Cancer Index; CC: case-control; CI: confidence interval; H/I test: HOXB13/IL17BR; HR: hazard ratio.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence: Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No decision-impact studies were identified that report clinical outcomes such as survival or recurrence.

Chain of Evidence: Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. 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. No studies comparing genetic test classifications with clinical risk prediction tools were identified. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported.

MammaPrint (70-Gene Signature)
Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

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) (see Table 20).[64] 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 20 details survival rates for the initial low- and high-risk groups, and for the subgroup analysis that separated an ultralow-risk group. This ultralow threshold was further validated by Delahaye et al (2017) using 3 separate cohorts, which reported 100% BCSS at 15 years of follow-up for patients in this ultralow risk category.[67]

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence: Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No decision-impact studies were identified that reported clinical outcomes such as survival or recurrence.

Chain of Evidence: Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. 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. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported.

Prosigna
Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

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).[61] 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 (eg, 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.[63] 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 displayed). The absence of CIs and comparison or reclassification of clinical predictors' prognosis limits any conclusions.

A subsequent publication by Sestak et al (2015)[62] combined samples of women with hormone receptor–positive, *HER2*-negative cancers from the ABSCG-8 and TransATAC studies included in the 2 prior publications.[61,63] 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 20). 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 23), 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%) fewer of 148 patients experiencing distant recurrence being treated, and (2) 15 (0.7%) 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 23. Classification and Reclassification Achieved by Adding ROR Score to the CTS

Distant Recurrence		CTS Low	Int	High	Total		CTS Low	Int	High	Total
ROR	Low	18	14	0	32	ROR + CTS	25	3	0	28
	Intermediate	7	31	7	45		8	53	0	61
	High	8	17	46	71		0	6	53	59
	Total	33	62	53	148		33	62	53	148
No Distant Recurrence		CTS Low	Int	High			CTS Low	Int	High	
ROR	Low	837	273	41	1151	ROR + CTS	1030	136	0	1166
	Intermediate	209	221	63	493		76	448	25	549
	High	60	137	148	345		0	47	227	274
	Total	1106	631	252	1989		1106	631	252	1989

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

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence: Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No decision-impact studies were identified that report clinical outcomes such as survival or recurrence.

Chain of Evidence: Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. Limitations (eg, 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.

The evidence gaps stated in Tables 24 and 25 are those notable in the current review; this is not a comprehensive gaps assessment.

Table 24. Relevance Gaps

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of FU[e]
Dubsky et al (2013)[60]	4. includes both node-negative and -positive patients			4. Reclassification of diagnostic or risk categories not reported	
Sestak et al (2013)[63]	4. includes both node-negative and -positive patients			4. Reclassification of diagnostic or risk categories not reported	
Sgroi et al (2013)[40]	4. includes both node-negative and -positive patients		3. No comparator (standard of care is clinical risk indicators)	1. Incremental improvement in applying risk category over standard is lacking 4. Reclassification of diagnostic or risk categories not reported	
Sgroi et al (2013)[65]	4. includes both node-negative and -positive patients		3. No comparator (standard of care is clinical risk indicators)	1. Incremental improvement in applying risk category over standard is lacking 4. Reclassification of diagnostic or risk categories not reported	
Zhang et al (2013)[41]				4. Reclassification of diagnostic or risk categories not reported	

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of FU[e]
Filipits et al (2014)[61]	4. includes both node-negative and -positive patients			4. Reclassification of diagnostic or risk categories not reported	
Esserman et al (2017)[64]	4. includes both ER-positive and ER-negative patients; some patients had 5 y of TAM and some patients had 2 y of TAM; some patients HER2-positive and some HER2-negative		3. No comparator (standard of care is clinical risk indicators)	1. Incremental improvement in applying risk category over standard is lacking 4. Reclassification of diagnostic or risk categories not reported	
Sestak et al (2015)[62]	4. includes both node-negative and -positive patients				
Sestak et al (2018)[38]	4. includes both node-negative and -positive patients			4. Reclassification of diagnostic or risk categories not reported	

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
ER: estrogen receptor; FU: follow-up; *HER2*: human epidermal growth factor receptor 2; TAM: tamoxifen.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 25. Study Design and Conduct Gaps

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Dubsky et al (2013)[60]	2. Convenience sample of women from another study					
Sestak et al (2013)[63]	2. Convenience sample of women from another study					
Sgroi et al (2013)[40]	2. Convenience sample of women from another study					
Sgroi et al (2013)[65]	2. Convenience sample of women from another study					
Zhang et al (2013)[41]	2. Convenience sample of women from another study					

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Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Filipits et al (2014)[61]	2. Convenience sample of women from another study					
Esserman et al (2017)[64]	2. Convenience sample of women from another study					
Sestak et al (2018)[38]	2. Convenience sample of women from another study					

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Section Summary: Extended Endocrine Therapy Beyond 5 Years for Oncotype DX, EndoPredict, the Breast Cancer Index, MammaPrint, and Prosigna

At least 3 RCTs have demonstrated survival improvements with extended tamoxifen. Results from trials using aromatase inhibitors after 5 years of endocrine therapy have reported inconsistent benefits in BCSS and duration of aromatase inhibitor use is uncertain. Recent trials comparing the use of aromatase inhibitors for different durations (2.5 years vs 5 years and 3 years vs 6 years) found no significant improvements in breast cancer–specific mortality or overall mortality among the different duration groups.

In the absence of direct evidence demonstrating clinical utility, the following need to be considered: (1) expected absolute benefit and certainty of benefit from extended endocrine therapy; (2) prognostic value of the test; and (3) incremental improvement of the test over clinical risk prediction algorithms:

1. Extended tamoxifen therapy provides an absolute reduction in breast cancer mortality of 2.8% between years 5 and 14, with no difference in overall mortality.[10] Despite credible studies, there are conflicting reports and uncertainty concerning aromatase inhibitors. Additional sources of uncertainty for extended endocrine therapy are the optimal combinations of tamoxifen and AIs, the optimal duration of extended therapy.
   Adverse events of endocrine therapy are significant. The ATLAS trial reported a cumulative risk of endometrial cancer of 3.1% in years 5 to 14 with tamoxifen treatment. Relative risk for pulmonary embolus was 1.9 (95% CI 1.1 to 3.1) in that same follow-up period. Aromatase inhibitors have increased cardiovascular and musculoskeletal adverse events compared with tamoxifen.
   In addition, noncompliance rates in women taking endocrine therapy are as high as 30%.[68]
2. All molecular tests (Oncotype DX, EPclin, BCI, MammaPrint, and Prosigna) have conducted nonconcurrent prospective studies and reported low distant recurrence rates (range, 1.4%-4.8%) and CIs (range, 0% to 7.9%).
3. Currently, physicians and patients use clinicopathogic parameters such as tumor size and nodal status to estimate risk of breast cancer recurrence while deciding on extended endocrine therapy. A clinical tool has been validated (CTS5). CTS5 is simple to use and incorporates clinical parameters (tumor size, tumor grade, age, and number of nodes)

that physicians and patients currently use when considering extended endocrine therapy. CTS5 identified 42% of women with less than a 1% per-year risk of distant recurrence who may be advised to safely forgo extended endocrine therapy.

Guidelines recommend that women and their physicians consider extended endocrine therapy, but do not categorically recommend extended endocrine therapy. Individual risk for adverse events will weigh heavily in women's decisions. Considerations are the magnitude of benefit expected from extended endocrine therapy, the assessment of individual risk of adverse events, tolerability of therapy, and the prognostic information available from existing clinical risk assessment tools. Thus it is unclear whether gene expression classification of recurrence risk, especially for low risk categories, adds sufficient incremental information to alter the calculation of risks and benefits of extended endocrine therapy.

The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. Reclassification of patients initially considered high risk by clinical criteria to a lower risk would allow avoidance of overtreatment of patients with significant side effects. However, it is unclear whether there is consistent improved reclassification of patients to lower risk categories.

Test Comparison Studies

Sestak et al (2018) compared the BCI, Oncotype DX, Prosigna, and EPclin using samples from the TransATAC RCT.[38] Distant recurrence rates for each test appear above in the respective categories for node-negative adjuvant chemotherapy, node-positive chemotherapy, and extended endocrine therapy, in which the low-risk categories of all 4 tests exhibited both low overall 10-year distant recurrence rates and low 5- to 10-year distant recurrence rates (within the threshold of <10%). Comparatively, among women who are considering adjuvant chemotherapy (N=591), EPclin classified most as low risk (n=429) compared with the other 3 tests, which classified 318 to 365 women as low risk. Among women who are considering extended endocrine therapy (N=535), EPclin classified most as low risk (n=393) compared with the other 3 tests, which classified 292 to 351 women as low risk.

Bosl et al (2017) compared MammaPrint with EndoPredict in 48 tumor samples—29 were node-negative, and 19 were node-positive.[69] 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.[40] 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)[70] examined cross-stratification between the BCI and Oncotype DX RS using the same data as Sgroi et al (2013).[40] 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 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 immunohistochemical 4 (IHC4) breast cancer algorithm.[45] 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.[71] 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.[72] 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.[73] 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.[74] Prat et al (2012) evaluated several gene expression tests, including Oncotype DX, PAM50, and MammaPrint, in 594 cases; they found all predictors were significantly correlated (Pearson r range, 0.36-0.79; p<0.001 for each comparison).[75]

Additional Applications and Other Tests
Based on a study by Badve et al (2008), which compared Oncotype DX estrogen and progesterone receptor results with traditional IHC results,[76] Genomic Health included 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 (Spearman ρ=0.91) than for estrogen receptor status (Spearman ρ=0.65), but worse concordance (at various cut points) for progesterone receptor status (99%) than for estrogen receptor status (88%).[77]

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.[78] 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

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 (ie, not predictive of treatment response).

Fitzal et al (2015) evaluated local recurrence using EndoPredict in breast tumor samples from 1324 patients who had participated in the ABCSG-8 trial (29% of enrolled patients), which compared adjuvant endocrine therapy regimens.[79] Most patients had node-negative, estrogen receptor–positive disease and received breast-conserving surgery and radiotherapy; approximately half 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
For all tests and all indications, relevant outcomes include disease-specific survival and changes in disease status.

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 at least 5-year distant recurrence rates or at least 5-year survival rates in node-negative women 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 BCI, 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 BCI 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, a study using a cancer registry cohort, and an RCT providing evidence for clinical utility. 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. The RCT (MINDACT) showed 5-year distance recurrence rates below the 10% threshold among patients identified as low risk. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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 95% 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 1 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 DCIS 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, BCI, 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 2 studies using data from the same previously conducted clinical trial. One analysis did not provide CIs and the other study reported a distant recurrence rate of 4.8% (95% CI, 2.9% to 7.9%) for the low-risk group. 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 2 analyses of archived tissue samples from 2 previously conducted clinical trials. The studies 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 to confirm 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 BCI, 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 several 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.

CLINICAL INPUT RECEIVED THROUGH PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

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

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

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network

Adjuvant Chemotherapy for Node-Negative Breast Cancer

Current guidelines from the National Comprehensive Cancer Network (NCCN) for breast cancer (v.2.2018)[2] provide a summary table assessing multigene assays to inform the addition of adjuvant systemic chemotherapy to adjuvant endocrine therapy (page BINV-M). The table shows that several genetic assays can be used to identify patients with node-negative breast cancer and low recurrence risk scores who may derive little benefit from chemotherapy. The NCCN category of evidence and consensus for the following assays is: level 1 for Oncotype DX and MammaPrint, and level 2A for Prosigna, EndoPredict, and the Breast Cancer Index. In the table, NCCN states that all the tests are prognostic, but only the Oncotype DX is predictive of response to chemotherapy in patients with node-negative breast cancer and is the preferred testing of the Network panel. In addition to the summary table, the following recommendation appears in an updated algorithm:

- "Strongly consider 21-gene RT-PCR assay" for node-negative, ER+ [estrogen receptor–positive], HER2- [human epidermal growth factor receptor 2–negative] breast cancer with "pT1, pT2, or pT3; and pN0" and tumor less than 0.5 cm. "Other prognostic multigene assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy."

Adjuvant Chemotherapy for Node-Positive Breast Cancer

The table discussed above in the NCCN guidelines for breast cancer (v.2.2018)[2] also provides information on the use of genetic assays to inform recurrence risk for patients with node-positive

(1 to 3 nodes) breast cancer. The level of evidence and consensus for Oncotype DX, MammaPrint, and EndoPredict for this population is 2A. In addition to the summary table, the following recommendation appears in an updated algorithm:

- "Consider multigene assay to assess prognosis and determine chemotherapy benefit" for node-positive, ER+, HER2- breast cancer with "pN1mi (≤2 mm axillary node metastasis) or N1 (<4 nodes). "There are few data regarding the role of multigene assays in women with four or more ipsilateral axillary lymph nodes. Decisions to administer adjuvant chemotherapy for this groups should be based on clinical factors." For N1mi and N1, "multigene assays are prognostic and not proven to be predictive of chemotherapy benefit but can be used to identify a low risk population that when treated with proper endocrine therapy may derive little absolute benefit from 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.[80] Table 26 shows the gene expression profiling biomarkers found to have demonstrated clinical utility to guide decisions on the need for adjuvant systemic therapy in women with early-stage invasive breast cancer and known estrogen and progesterone and *HER2* status. The guidelines did not endorse any test for decision-making to determine the length of tamoxifen treatment.

Table 26. Guidelines for Estrogen and Progesterone Receptor–Positive and *HER2*-Negative Breast Cancer

Test	Recommendation	QOE	SOR
Node-negative			
Oncotype DX	Clinician may use the 21-gene recurrence score to guide decisions on adjuvant systemic chemotherapy	High	Strong
EndoPredict	Clinician may use the 12-gene risk score to guide decisions on adjuvant systemic chemotherapy	Intermediate	Moderate
Breast Cancer Index	Clinician may use the Breast Cancer Index to guide decisions on adjuvant systemic therapy	Intermediate	Moderate
MammaPrint	• Clinician may use the 70-gene assay to guide decisions on adjuvant systemic therapy in women with high clinical risk per MINDACT categorization • Clinician should not use the 70-gene assay to guide decisions on adjuvant systemic therapy in women with low clinical risk per MINDACT categorization	High	Strong
Prosigna	Clinician may use the PAM50 risk of recurrence score, in conjunction with other clinicopathologic variables, to guide decisions on adjuvant systemic therapy	High	Strong
Node-positive (1-3 nodes)			
MammaPrint	Clinician may use the 70-gene assay to guide decisions on adjuvant systemic therapy in women with high clinical risk per MINDACT categorization	High	Moderate

HER2: human epidermal growth factor receptor 2; QOE: quality of evidence; SOR: strength of recommendation.

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.[81] Table 27 summarizes guidelines on the use of biomarkers in patients with invasive breast cancer.

Table 27. Guidelines on the Use of Biomarkers in Patients with Invasive Breast Cancer

Test	Recommendation	LOE	SOR
Oncotype DX	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	1B	A
MammaPrint	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	1A	A
Prosigna	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	1B	A
EndoPredict	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	1B	A
Breast Cancer Index	For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy in patients with ER-positive/HER2-negative, lymph node-negative disease	1B	A

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
In 2017, an international expert Panel, including members from the United States, convened for the 15th St. Gallen International Breast Cancer Conference. The Panel reviewed current evidence on locoregional and systemic therapies for early breast cancer. Table 28 summarizes relevant recommendations.

Table 28. Therapies by Breast Cancer Diagnosis

Breast Cancer Group	Recommendation
Adjuvant chemotherapy for patients with node-negative breast cancer	The Panel endorsed the following gene expression assays for guiding the decision on adjuvant chemotherapy in node-negative cancers: 21-gene recurrence score, the 70-gene signature, the PAM50 ROR score, the EPclin score, and the Breast Cancer Index.[82]
Adjuvant chemotherapy for patients with node-positive breast cancer	"The Panel did not uniformly endorse the use of gene expression signatures for making treatment decisions regarding adjuvant chemotherapy in node-positive cases."[82]
Extended endocrine therapy for patients recurrence free at 5 years	"The Panel did not recommend the use of gene expression signatures for choosing whether to recommend extended adjuvant endocrine treatment, as no prospective data exist and the retrospective data were not considered sufficient to justify the routine use of genomic assays in this setting."[82]

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this policy are listed in Table 29.

Table 29. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT00310180	Program for the Assessment of Clinical Cancer Tests (PACCT-1): Trial Assigning Individualized Options for Treatment: The TAILORx Trial[84]	11,248	Mar 2018 (ongoing)
NCT00433589[a]	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	6600	Mar 2020

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NCT No.	Trial Name	Planned Enrollment	Completion Date
	Common Clinical-Pathological Criteria in Selecting Patients for Adjuvant Chemotherapy in Breast Cancer With 0 to 3 Positive Nodes		
NCT01272037	A Phase III, Randomized Clinical Trial of Standard Adjuvant Endocrine Therapy +/- Chemotherapy in Patients With 1-3 Positive Nodes, Hormone Receptor-Positive and HER2-Negative Breast Cancer With Recurrence Score (RS) of 25 or Less. RxPONDER: A Clinical Trial Rx for Positive Node, Endocrine Responsive Breast Cancer	10,000	Feb 2022
NCT02653755[a]	The PRECISION Trial (Profiling Early Breast Cancer for Radiotherapy Omission): a Phase II Study of Breast-Conserving Surgery Without Adjuvant Radiotherapy for Favorable Risk Breast Cancer	690	Jun 2023
NCT02400190	The IDEA Study (Individualized Decisions for Endocrine Therapy Alone)	202	Mar 2026
NCT03503799	Prospective Assessment of Disease Progression in Primary Breast Cancer Patients Undergoing EndoPredict Gene Expression Testing – a Care Research Study	1200	May 2031
Unpublished			
NCT01501487[a]	MINT: Multi-Institutional Neo-Adjuvant Therapy MammaPrint Project	226	Jun 2018 (completed)
NCT02395575[a]	Prospective Study Evaluating the Clinical Impact of the Breast Cancer Intrinsic Subtype-Prosigna Test (Assay) in the Management of Early Stage Breast Cancers	200	Dec 2017 (completed)
NCT02627703[a]	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	80	Dec 2017 (unknown)

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

CPT/HCPCS

81518	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy
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
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 reporting as a recurrence risk score
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
81599	Unlisted multianalyte assay with algorithmic analysis

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

0008M   Oncology (breast), mRNA analysis of 58 genes using hybrid capture, on formalin-fixed paraffin-embedded (FFPE) tissue, prognostic algorithm reported as a risk score

ICD-10 Diagnoses

Code	Description
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.021	Malignant neoplasm of nipple and areola, right male breast
C50.022	Malignant neoplasm of nipple and areola, left male breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast

REVISIONS

11-09-2011	In the Policy section:
	 • Revised the policy language as indicated below to the current language:
	 "Patient must meet all the following criteria:
	     A Gene Expression Survey such as Oncotype DX™, is a diagnostic test designed to assist in the decision making in regards to chemotherapy treatments based on the possibility of the recurrence of breast cancer in those women with newly diagnosed, early-stage breast cancer. The cancer diagnosis has all of the following characteristics:
	     • Estrogen-receptor positive (ER+)
	     • Newly diagnosed
	     • Node negative
	     • Stage I or II (based on size only—over 2 cm)"

	In the Policy Guidelines section: • Added the following: "According to the American Society of Clinical Oncology-College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer, "a positive HER2 result is IHC [immunohistochemistry] staining of 3+ (uniform, intense membrane staining of >30% of invasive tumor cells), a fluorescent in situ hybridization (FISH) result of more than six HER2 gene copies per nucleus or a FISH ratio (HER2 gene signals to chromosome 17 signals) of more than 2.2; a negative result is an IHC staining of 0 or 1+, a FISH result of less than 4.0 HER2 gene copies per nucleus, or FISH ratio of less than 1.8. Equivocal results require additional action for final determination." (1)"

	Updated the Rationale section.
	Updated the Reference section.
04-12-2013	Updated Description section.
	In Policy section: ▪ In Item D, revised the following "patients who are lymph node positive" to read "patients with positive lymph nodes". ▪ In Item D, inserted "or patient with bilateral disease" to read "patients with positive lymph nodes or patient with bilateral disease," ▪ Added Item E, "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 DCIS) to inform treatment planning following excisional surgery is considered experimental / investigational." ▪ In Item F, revised the following "The use of other gene expression assays (e.g., MammaPrint, Mammostrat, or the THEROS Breast Cancer Index[SM]) for any indication is considered experimental / investigational." to read "The use of other gene expression assays (e.g., MammaPrint, Mammostrat Breast Cancer Test, the Breast Cancer Index, The BreastOncPx, NexCourse Breast IHC4, or PAM50 Breast Cancer Intrinsic Classifier) for any indication is considered experimental / investigational."
	Updated Rationale section.
	In Coding section: ▪ Added diagnosis code, 233.0
	Updated Reference section.
03-27-2014	Updated Description section.
	In Policy section: ▪ Added new Item D, "The use of gene expression assays in men with breast cancer is considered medically necessary. ▪ In Item G, added "Breast PRS and EndoPredict" to read "…or PAM50 Breast Cancer Intrinsic Classifier, Breast PRS and EndoPredict) for any indication is considered experimental / investigational." ▪ Added Item H, "The use of gene expressional assays to molecularly subclassify breast cancer (e.g., BluePrint) is considered experimental / investigational." ▪ Added Item I, "The use of gene expression assays for quantitative assessments of ER, PR, and HER2 overexpression (e.g., TargetPrint) is considered experimental / investigational."
	Updated Rationale section.
	In Coding section: ▪ Added ICD-10 Diagnosis *(Effective October 1, 2014)*
	Updated Reference section.
01-01-2015	Policy posted 01-16-2015
	In Coding section: ▪ Added CPT Codes: 81519 (Effective January 1, 2015), 0008M (Effective July 1, 2014) ▪ Added CPT Code: 84999 (applies to applicable services before January 1, 2015)
04-28-2015	Title of Policy changed from "Gene Expression Assay for Breast Cancer Treatment."
	Updated Description section.
	In Policy section: ▪ In Item A, added "invasive" and "all of", to read, "The use of the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (i.e., Oncotype DX®) to determine recurrence risk for deciding whether or not to undergo adjuvant chemotherapy may be considered medically necessary in women with primary, invasive breast cancer meeting all of the following characteristics:" ▪ In Item E, added "invasive", to read, "All other indications for the 21-gene RT-PCR assay (i.e., Oncotype DX®), including determination of recurrence risk in invasive

	breast cancer patients with positive lymph nodes or patient with bilateral disease, are considered experimental / investigational." ▪ In Item G, added "70-gene signature" and "Prosigna™" and removed "or PAM50 Breast Cancer Intrinsic Classifier," to read, "The use of other gene expression assays (e.g., MammaPrint® 70-gene signature, Mammostrat® Breast Cancer Test, the Breast Cancer Index^SM, the BreastOncPx™, NexCourse® Breast IHC4, Prosigna™, BreastPRS™, and EndoPredict™) for any indication is considered experimental / investigational." In Policy Guideline section: ▪ In Item 1, added "0.6" and removed "0.3", to read, "Unfavorable features that may prompt testing in tumors from 0.6 to 1 cm in size include the following: angiolymphatic invasion, high histologic grade, or high nuclear grade." ▪ In Item 3, removed, "a positive HER2 result is IHC [immunohistochemistry] staining of 3+ (uniform, intense membrane staining of >30% of invasive tumor cells), a fluorescent in situ hybridization (FISH) result of more than six HER2 gene copies per nucleus or a FISH ratio (HER2 gene signals to chromosome 17 signals) of more than 2.2; a negative result is an IHC staining of 0 or 1+, a FISH result of less than 4.0 HER2 gene copies per nucleus, or FISH ratio of less than 1.8. Equivocal results require additional action for final determination.(1)" and added ",(1) defines positive, negative, and equivocal HER2 test results as shown in table 2", to read, "According to the American Society of Clinical Oncology-College of American Pathologists G guideline, "Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer,"(1) defines positive, negative, and equivocal HER2 test results as shown in Table 2." ▪ Added Table 2
	Updated Rationale section.
	In Coding section: ▪ Removed " There are no specific CPT codes for these laboratory tests. Effective 1/1/06, an S code was designated for this test: S3854," and added, "Effective 07/01/14, there is a CPT multianalyte assay with algorithmic analysis (MAAA) administrative code specitic to the Prosigna test: 0008M. Effective January 1, 2015, there is a specitic CPT MAAA code for Oncotype DX: 81519. Effective January 1, 2006, an S code was designated for this test: S3854. The other tests mentioned above would be reported with an unlisted CPT code such as 81599."
	Updated References section.
09-29-2015	Updated Description section.
	In Policy section: ▪ In Item A, removed "or not", to read "The use of the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (i.e., Oncotype DX®) to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy may be considered medically necessary in women with primary, invasive breast cancer meeting ALL of the following characteristics:" ▪ In Item A 1, removed "non-fixed", to read "unilateral tumor; AND" In Policy Guidelines: ▪ In Item 3, removed "According to the", and added "The current (2013)", to read "The current (2013) American Society of Clinical Oncology-College of American Pathologists guideline…"
	Updated Rationale section.
	Updated References section.
01-01-2016	In Coding section: ▪ Removed HCPCS code S3854.
07-01-2016	In Coding section: ▪ Added HCPCS code S3854.

	▪ Revising coding bullets.
01-04-2017	Updated Description section.
	In Policy section: ▪ In Item A, added "Endopredict, the Breast Cancer Index^{SM}, and Prosigna" to read, "The use of the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (ie, Oncotype DX®), EndoPredict, the Breast Cancer IndexSM, 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:" ▪ In Item F, added "All other indications for the 21-gene RT-PCR", "(ie, Oncotype DX®)", and "including determination of recurrence risk in invasive breast cancer patients with positive lymph nodes, patients with bilateral disease, or to consider length of treatment with tamoxifen, are" and removed "The use of other gene expression", "e.g., MammaPrint® 70-gene signature, Mammostrat® Breast Cancer Test,", "the BreastOncPx™, NexCourse® Breast IHC4,", "Breast PRS™", and "for any indication is" to read, "All other indications for the 21-gene RT-PCR assay (i.e., Oncytope DX®), Endopredict™, the Breast Cancer Index^{SM}, and Prosigna®, including determination of recurrence risk in invasive breast cancer patients with positive lymph nodes, patients with bilateral disease, or to consider length of treatment with tamoxifen, are considered experimental / investigational." ▪ In Item G, added "Breast" and "Score" to read, "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 (ie, Oncotype DX® Breast DCIS Score) to inform treatment planning following excisional surgery is considered experimental / investigational." ▪ Added new Item H, "Use of 70-gene signature (MammaPrint®) for any indication is considered experimental / investigational." ▪ In new Item I (previous Item H), added "in conjunction with MammaPrint® or alone" and removed "gene expression assays to molecularly subclassify breast cancer (e.g.," to read, "The use of BluePrint® in conjunction with MammaPrint® or alone is considered experimental / investigational." ▪ Removed previous Item I, "The use of gene expression assays for quantitative assessment of ER, PR, and HER2 overexpression (e.g., TargetPrint®) is considered experimental / investigational."
	Updated Rationale section.
	In Coding section: ▪ Added CPT code: 81599. ▪ Removed CPT code: 84999. ▪ Updated coding bullets.
	Updated References section.
	Added Appendix section.
10-28-2017	Updated Description section.
	In Policy section: ▪ In Item A, removed "women" and added "individuals" to read, "The use of the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (ie, Oncotype DX®), EndoPredict, the Breast Cancer Index, and Prosigna to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy may be considered medically necessary in individuals with primary, invasive breast cancer meeting ALL of the following characteristics:" ▪ Removed Item D, "The use of gene expression assays in men with breast cancer is considered medically necessary."
	Updated Rationale section.
	In Coding section: ▪ Updated coding bullets.

	Updated References section.
01-01-2018	Updated Description section.
	In Policy section: ▪ Removed Item D, "All other indications for the 21-gene RT-PCR assay (ie, Oncotype DX), including determination of recurrence risk in invasive breast cancer patients with positive lymph nodes or patients with bilateral disease, are considered experimental / investigational."
	Updated Rationale section.
	In Coding section: ▪ Added CPT codes: 81520, 81521. ▪ Removed coding bullets. ▪ Removed ICD-9 codes.
	Updated References section.
08-01-2018	Updated Rationale section.
	Updated References section.
01-01-2019	In Coding section: ▪ Added new CPT code: 81518
02-01-2019	Policy published 01-04-2019 with an effective date of 02-01-2019.
	Updated Description section.
	In Policy section: ▪ In Item A, added "MammaPrint" and removed "the 21-gene reverse transcriptase-pomymerase chain reaction (RT-PCR) assay" to read, "The use of Oncotype DX, 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 individuals with primary, invasive breast cancer meeting ALL of the following characteristics:" ▪ In Item D, added "MammaPrint" and removed "the 21-gene RT-PCR assay" to read, "All other indications for 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 length of treatment with tamoxifen, are considered experimental / investigational." ▪ Removed previous Item F, "Use of 70-gene signature (MammaPrint) for any indication is considered experimental / investigational." ▪ Removed Policy Guidelines.
	Updated Rationale section.
	Updated References section.
	Removed Appendix section.

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