2.04.36	Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer		
Original Policy Date:	December 1, 2005	**Effective Date:**	January 1, 2021
Section:	2.0 Medicine	**Page:**	Page 1 of 66

Policy Statement

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

I. Patient has unilateral tumor
II. Patient is hormone receptor-positive (i.e., estrogen receptor-positive or progesterone receptor [PR]-positive)
III. Patient is human epidermal growth factor receptor 2 (*HER2*)-negative
IV. Documentation of **one or more** of the following:
    A. Tumor size 0.6 to 1 centimeter (cm) with moderate or poor differentiation or unfavorable features
    B. Tumor size larger than 1 cm
V. Documentation of **one or more** of the following:
    A. Patient is node-negative (lymph nodes with micrometastases [less than or equal to 2 millimeters (mm) in size] are considered node-negative for this policy statement)
    B. Up to three positive nodes when the test is for MammaPrint or Oncotype DX AND the patient is in stage T1, T2 or operable T3 AND at high clinical risk
VI. Patient will be treated with adjuvant endocrine therapy (e.g., tamoxifen, aromatase inhibitors)
VII. The test result aids the patient in deciding on chemotherapy (i.e., when chemotherapy is a therapeutic option)
VIII. Ordered within 6 months after diagnosis, because the value of the test for making decisions regarding delayed chemotherapy is unknown

The following conditions are considered **investigational:**

I. All other indications for the 21-gene RT-PCR assay (i.e., Oncotype DX®), EndoPredict®, the Breast Cancer Index℠, MammaPrint®, and Prosigna®, including determination of recurrence risk in invasive breast cancer patients with positive lymph nodes (except Mammaprint when there are less than 4 positive nodes), patients with bilateral disease, or to consider the length of treatment with tamoxifen
II. Use of a subset of genes from the 21-gene RT-PCR assay for predicting recurrence risk in patients with noninvasive ductal carcinoma in situ (i.e., Oncotype DX® Breast Ductal Carcinoma in Situ [DCIS] Score) to inform treatment planning after excisional surgery
III. The use of BluePrint® (either in conjunction with MammaPrint or alone)
IV. The use of Insight TNBCtype to aid in making decisions regarding chemotherapy in women with triple-negative breast cancer
V. Use of gene expression assays in men with breast cancer

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Note: The multi-gene RT-PCR assay Oncotype DX®, EndoPredict®, the Breast Cancer Index℠, MammaPrint®, and Prosigna® assays should only be ordered on a tissue specimen obtained during surgical removal of the tumor and after subsequent pathology examination of the tumor has been completed and determined to meet the above criteria (i.e., the test should not be ordered on a preliminary core biopsy). The test should be ordered in the context of a physician-

patient discussion regarding risk preferences when the test result will aid in making decisions regarding chemotherapy.

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

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

In the MINDACT trial (Cardoso 2016), low versus high clinical risk was determined using the Adjuvant! Online tool (version 8.0 with HER2 status, www.adjuvantonline.com). The Adjuvant tool includes factors for age, comorbidities, ER status, tumor grade and size and number of positive nodes. In MINDACT, ER-positive, HER2-negative, node-positive (1 to 3 nodes) patients were classified as high clinical risk if they met any of the following additional criteria:

- Grade 1: well differentiated; tumor size, 3.1 to 5 cm
- Grade 2: moderately differentiated; tumor of any size
- Grade 3: poorly differentiated or undifferentiated; tumor of any size

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.

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

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

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

Result	Immunohistochemistry	Fluorescence In Situ Hybridization
Negative	0 or 1+: No staining or faint/barely perceptible, incomplete membrane staining in any proportion of tumor cells	Ratio of *HER2*/CEP17[a] <2.0 AND Average *HER2* CN <4.0 signals per cell Or Average *HER2* CN <4.0 signals per cell[b]
Positive	3+: At least 10% of tumor cells exhibit complete, intense, circumferential membrane staining	Ratio of *HER2*/CEP17 >2.0 Or Ratio of *HER2*/CEP17 is <2.0 AND Average *HER2* CN ≥6.0 signals per cell Or Average *HER2* CN ≥6.0 signals per cell[b]
Equivocal	2+: Circumferential membrane staining that is either: • incomplete and/or weak/moderate within >10% of tumor cells, or • complete and intense within ≤10% of tumor cells	Ratio of *HER2*/CEP 17 <2.0 AND Average *HER2* CN ≥4.0 and <6.0 signals per cell Or Average *HER2* CN ≥4.0 and <6.0 signals per cell[b]

ASCO: American Society of Clinical Oncology; CAP: College of American Pathologists; CEP: chromosome enumeration probe; CN: copy number; HER2: human epidermal growth factor receptor 2.

[a] CEP 17 is a centromeric probe for chromosome 17 (internal control probe).
[b] Signals per cell for test systems without an internal central probe.

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

Coding
The following PLA CPT code is specific for Insight TNBCtype™ test, which was produced by Insight Molecular Labs:

- **0153U:** Oncology (breast), mRNA, gene expression profiling by next-generation sequencing of 101 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a triple negative breast cancer clinical subtype(s) with information on immune cell involvement

The following CPT code is specific for EndoPredict® test, which was produced by Myriad Genetic Lab:

- **81522:** Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score

The following CPT multianalyte assay with algorithmic analysis (MAAA) code is for the screening of metastatic recurrence and is specific for Breast Cancer Index (BCI):

- **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

There is a specific CPT MAAA code for Oncotype DX®:

- **81519**: Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score

The following CPT code is specific to the Oncotype DX® Breast DCIS Score™ Test, which was produced by Genomic Health, Inc.:

- **0045U:** Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score

The following CPT MAAA category I code is specific to the Prosigna® test *that replaced the code 0008M*:

- **81520**: Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score

The following CPT MAAA category I code is specific to the Mammaprint® test:

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

There is a specific HCPCS S code for this testing:

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

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

- **81479**: Unlisted molecular pathology procedure

- **81599**: Unlisted multianalyte assay with algorithmic analysis

Description

Laboratory tests have been developed to detect the expression, via messenger RNA, of different genes in breast tumor tissue and combine the results to determine prognosis in patients with 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 or triple-negative (estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2) breast cancer (TNBC), or to recommend extended endocrine therapy in patients who are recurrence-free at 5 years. This report summarizes the evidence for 6 tests and is organized by indication.

Related Policies

- N/A

Benefit Application

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

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

Regulatory Status

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

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

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

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

Rationale

Background

Newly Diagnosed Breast Cancer

Most women with newly diagnosed breast cancer in the U.S. present with the 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 levels 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 4 decision points:

1. ***The decision to pursue adjuvant chemotherapy following locoregional therapy, with or without neoadjuvant chemotherapy, based on the predicted risk of recurrence, for women who are hormone receptor-positive but HER2-negative.*** The use of adjuvant chemotherapy reduces the risk of breast cancer recurrence but carries risks of systemic toxicity. The risk: benefit ratio must be considered for each patient, with a higher likelihood of net health benefits for patients with a greater baseline predicted 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, BCBSA focuses specifically on patients without *HER2* expression.
2. ***The decision to pursue extended adjuvant endocrine therapy from 5 to 10 years for women who are hormone receptor-positive but HER2-negative and who have survived without a recurrence for 5 years.*** For patients with hormone receptor-positive tumors, the use of adjuvant endocrine therapy (tamoxifen and/or an aromatase inhibitor [AI], with or without ovarian suppression) for 5 to 10 years after an initial diagnosis has support in clinical practice. Support for extended endocrine therapy beyond the initial 5 years is inconsistent across various guidelines. The guidelines from the National Comprehensive Cancer Network (v.6.2020) include various recommendations and considerations, based on menopausal status at diagnosis and after 5 years of therapy, and on prior therapy history (see Table 27 in the Supplemental Information section). The guidelines also note that the optimal duration of AIs is uncertain.[2] The American Society for Clinical Oncology's updated guidelines (2018) vary based on recurrence risk and nodal status (see Supplemental Information section).[3,4]
3. ***The decision to pursue adjuvant radiotherapy in women with ductal carcinoma in situ.*** 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.
4. ***The decision to pursue neoadjuvant chemotherapy in women with Triple-Negative Breast Cancer (TNBC).*** In women with TNBC, pathological complete response has been found to be heterogenous in the neoadjuvant setting and has been associated with prolonged overall survival. For example, although TNBC tends to be more aggressive than other breast cancer types and confers a less favorable prognosis, previous research has suggested that the 20-40% of women with TNBC who achieve pathological complete response may achieve a similar long-term survival prognosis as patients with non-TNBC breast cancers.[5] This heterogeneity suggests that there may be subtypes of women with TNBC that significantly differ in their likelihood of response to neoadjuvant chemotherapy and differ in their risk: benefit treatment considerations.

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-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%, 10-year risk of recurrence with tamoxifen alone, which means that approximately 85% of these patients could avoid the toxicity of adjuvant cytotoxic chemotherapy if they could be accurately identified. Conventional risk classifiers (e.g., Adjuvant! Online) estimate recurrence risk by considering criteria such as tumor size, type, grade, and histologic characteristics; hormone receptor status; and the number of affected lymph nodes. Consensus guidelines for defining receptor status exist[6.]; 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

Nodes	Recurrence, Hazard[a] (SE), %				
	Years				
	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.]
SE: standard error.
[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=21457 patients), found that 5 years of tamoxifen in estrogen receptor-positive disease reduced the relative risk of recurrences by almost 50% over 10 years; breast cancer mortality was decreased by 29% through 15 years.[7.]

Early randomized trials of extended tamoxifen treatment-Tormey et al (1996; total n=194 patients),[8.] the National Surgical Adjuvant Breast and Bowel Project (Fisher et al [2001]; total n=1172 patients),[9.] and the Scottish Cancer Trials Breast Group (Stewart et al [2001]; total n=342 patients)[10.] had mixed findings. However, more recent available trial evidence suggests that ten 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 Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial, which compared 5 and 10 years of tamoxifen,[11] and the subsequent Long-term Effects of Continuing Adjuvant Tamoxifen to 10 Years versus Stopping at 5 Years (aTTom) trial (reported in abstract form)[12] 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 OS (see Table 2).

Several trials have compared survival outcomes in women using extended Aromatase inhibitors vs placebo following several years of tamoxifen,[13,14,15,16] and 2 trials compared the use of extended AIs for different durations (3 years vs 6 years[17] and 2.5 years vs 5 years[18]) (see Table 2). No differences in OS were detected between the AI groups and with the placebo groups. Differences in breast cancer-specific survival were inconsistent. Differences in disease-specific survival and OS were not detected among patients receiving AIs for different lengths of time.

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 AIs include musculoskeletal side effects (e.g., carpal tunnel syndrome, bone pain, bone fractures). In meta-analyses comparing tamoxifen and AIs, results showed an increased risk in cardiovascular events with AIs relative to tamoxifen.[19,20] Women treated with AIs 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)[11]	6,846 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)[12]	6,953 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)[13]	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

Study	Population	Comparators	Breast Cancer-Specific Mortality		Overall Mortality	
			Breast Cancer-Specific Survival		Overall Survival	
IDEAL (2018)[18.]	1,824 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)[17.]	1,912 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)[16.]	1,598 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 crossed over to exemestane after unblinding	48 Months • ITT: 91% exemestane vs 89% placebo	0.07		
NCIC CTG MA.17 trial (2003, 2005)[14.15.]	5,187 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, 2 trials were presented in early 2017 evaluating extended endocrine therapy in postmenopausal women (NSABP-42 [NCT00382070]: 10 years vs 5 years of letrozole; and IDEAL [NTR3077] 10 years vs 7.5 years of letrozole) did not meet their primary endpoints.

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 the determination of treatment-biomarker interactions that may be clinically important. In some clinical scenarios, demonstration of a treatment-biomarker interaction is not critical, because the decision to withhold chemotherapy in a low-risk group (to avoid chemotherapy-related morbidity) does not require the presence of a biomarker-treatment interaction. The study must generate an absolute estimate of outcomes in the patient group of interest that would result in a change in management (e.g., withholding of chemotherapy), and the study must have sufficient precision (narrow confidence intervals). Results of the same test across studies should show the consistency of results and more than 1 study demonstrating the desired result should be available. Simon et al (2009) have proposed that at least 2 Simon et al (2009) category B studies showing results consistent with clinical utility are necessary to demonstrate adequate evidence of a biomarker.[22.] Simon et al (2009) 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.]

Literature Review

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 in Tumor Tissue

Clinical Context and Test Purpose

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

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 PICO was used to select literature to inform this review.

Populations

The populations of interest include:

- Women with early-stage node-negative or node-positive, hormone receptor-positive but HER2-negative, invasive breast cancer considering adjuvant chemotherapy;
- Women with DCIS considering radiotherapy; and

- Women with early-stage node-negative, hormone receptor-positive but HER2-negative, invasive breast cancer, recurrence-free at 5 years considering extended endocrine therapy; and
- Women with TNBC considering neoadjuvant chemotherapy

Interventions

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

- 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. However, the assays are derived from analysis of the primary tumor only which was collected before endocrine therapy.
- For patients with TNBC, the assays would be performed following the diagnosis of TNBC, when patients are considering neoadjuvant chemotherapy.

In clinical scenarios involving breast cancer, accurate assessment of prognosis may affect the decision to offer certain treatments. Recently, several groups have identified panels of gene expression markers ("signatures") that appear to predict the baseline risk of invasive breast cancer recurrence after surgery, radiotherapy, and endocrine therapy (for hormone receptor-positive tumors). Several gene expression tests commercially available in the U.S. are listed in Table 3. If these panels are more accurate risk predictors than current clinical 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 the 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 2 (*HER2)* status. The proposed clinical utility of these tests varies by the clinical context; these specific indications are discussed in this review:

- 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.
- 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.
- Prognosis and/or prediction of treatment response in patients with ductal carcinoma in situ for the purpose of determining whether patients can avoid radiotherapy.
- 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.
- Prognosis and/or prediction of treatment response in patients with TNBC considering neoadjuvant chemotherapy for the purpose of determining whether patients can avoid neoadjuvant chemotherapy.

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 events. If a patient subgroup can be defined that has an extremely low-risk of distant recurrence, or a subgroup can be defined that does not respond to the treatment, then

the additional treatment can be forgone with little effect on cancer outcome due to the low-risk of poor outcome or lack of response to treatment.

Table 3. Gene Expression Tests Reporting Recurrence Risk for Breast Cancer Considered Herein

Test	Manufacturer	Description
Oncotype DX®	Genomic Health	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	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)
Insight TNBCtype™	Insight Genetics	Uses next-generation sequencing of 101 genes to generate 5 molecular subtypes, as well as a complementary immunomodulatory classifier to help predict response to immuno-oncology therapies. This may include directing selection and combination of chemotherapies, as well as to support development of novel TNBC targeted therapeutics and diagnostics

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

Additional commercially available tests may provide 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 as a molecular subtype test. The BluePrint® 80-gene molecular subtyping assay is offered in combination with MammaPrint to augment predictive data about the response to chemotherapy.

Comparators

The comparators of interest for all assays are clinical risk prediction algorithms.

For adjuvant chemotherapy, a conventional risk classifier (e.g., 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.
- In patients with TNBC, molecular subtype classifications based on likelihood of response to neoadjuvant chemotherapy may inform risk: benefit considerations and aid in shared decision making about whether to undergo or forgo treatment.

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 OS than disease-free survival. Disease-free survival also includes local recurrence, which has a much better treatment prognosis than the 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] The Early Breast Cancer Trialists' Collaborative Group (2012) conducted a patient data meta-analysis of 123 trials (n>100000 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 the requirement for the 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 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 a 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 et al (2005) 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 et al (2005).

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 is no such consensus on a specific recurrence threshold that is acceptable for avoiding extended adjuvant endocrine therapy.

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,]

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires a 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 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).

Low-Risk Threshold (Recurrence Scores ≤10)

BCBSA identified 4 studies with 10 year outcomes meeting selection criteria for the low-risk category (see Appendix 1).[32,33,34,35,] The studies derive from 3 completed randomized trials and thus are all Simon et al (2009) 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,] The trial evaluated outcomes at 5 years. It is among the few Simon et al (2009) category A studies available. In it, women with node-negative, estrogen receptor-positive, *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 10253 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 in 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 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, Trial Assigning Individualized Options for Treatment to evaluate the 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 in TAILORx[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 the patients were classified as low-risk. The prospective study by Sparano et al (2015), 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 OS.[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 (2016) and 68% in Filipits et al (2011).

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 (2011) 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 (2016) reported distant recurrence-free rates of 94.1% in the EPclin low-risk group and 80.0% in the EPclin high-risk group.

Sestak et al (2019) reported results of an analysis of the performance of EndoPredict to predict chemotherapy benefit.[40] The analysis included 3746 women; 2630 patients received 5 years of ET alone (from ABCSG-6/8, TransATAC trials) and 1116 patients received ET + C (from GEICAM 2003-02/9906 trial). There was a significant positive interaction between EPclin as a continuous measure and treatment group for the outcome of the 10 year DR rate (interaction p=0.022). Although the comparison is indirect, it may suggest that a high EPclin score can predict chemotherapy benefit in women with ER-positive, HER2-negative disease.

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 the small absolute benefit of adjuvant chemotherapy. In these

studies, over half of the patients were classified as 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).[41,42] Some *HER2*-positive patients were included in both studies but the number was not provided. Sgroi et al (2013)[41] and Sestak et al (2018)[38] analyzed patients receiving anastrozole or tamoxifen in the ATAC trial. This trial constitutes a Simon et al (2009) 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, 1 deriving from a clinical trial and another from patient registries.[42] 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 a low risk of disease recurrence at 10 years. The Sgroi et al (2013) and Sestak et al (2018) 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 et al (2013) 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)[42] (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)[42] (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)[41.] (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.

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 et al (2009) category B. The findings from the multicenter registry are Simon et al (2009) 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.[43.] The study sample was derived from 3 separate cohorts in cancer registry studies (Simon et al [2009] 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 a 10 year distant recurrence risk below 10%. All other combinations of clinical risk and MammaPrint risk had 10 year recurrence risks greater than 10%. This pattern would suggest that a clinical strategy of using MammaPrint only in those with 2 clinical risk scores indicating low-risk would identify patients with a 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 optional randomization for an additional 3 years to tamoxifen or no treatment.[44.] 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)[44.,a]	538	• Low-risk, with tamoxifen: 199 (37) • Low-risk, without tamoxifen: 172 (32)	• 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)

Study (Source of Patients)	N	MP Risk Score Group, n (%)	10-Year DMFS (95% CI), %	20-Year BCSS (95% CI), %
		• High-risk, with tamoxifen: 82 (15) • High-risk, without tamoxifen: 85 (16)		
		Clinical Risk Score Group and MP Risk Score Group, n (%)	**10-Year Distant Recurrence (95% CI), %**	
Bueno-de-Mesquita et al (2011)[43] (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 Microarray In Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy (MINDACT) trial (Cardoso et al [2016]) is a prospectively designed trial evaluating MammaPrint, with additional randomized components (see Table 10).[45] 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 endpoint 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 endpoint 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.

While trial entry criteria included patients with node-positive, estrogen receptor-negative, or *HER2*-positive breast cancer, 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 the 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)[45.] (MINDACT trial)	4225	• Clin low/MP low: 58 • Clin low/MP high: 11 • Clin high/MP low: 17 • Clin high/MP high: 14[a]	• 2.4 (1.8 to 3.1) • 6.1 (3.9 to 9.4) • 4.5 (2.4 to 8.4) • 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]), and 1, category B study (van't Veer et al [2017]). The Simon et al (2009) category B study provided 10-year distant recurrence outcomes. 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 et al (2009) 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 (studies are classed as Simon et al [2009] category B).[46.47.38.] 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.).[46.] All studies reported distant recurrence rates below 5%, with the CIs not exceeding 10%. In the 2 studies reporting the proportion of patients classified as low-risk, more than 47% of patients were classified as 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)[47.] (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)[46.] (ATAC trial)	739	59	33	8	4.8 (NR)	13.8 (NR)	30.2 (NR)
Sestak et al (2018)[38.] (ATAC trial)	591	54	30	16	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 et al (2009) 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 clinical validity 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 multiple publications from 3 studies,[48,49,38,50,51.] Prosigna risk of recurrence (ROR)[52.] in 1 study, and EndoPredict in 2 studies. Albain et al (2010) also explored a possible role for Oncotype DX in predicting chemotherapy benefit.[48.] 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)[48.],a	148	145 (98)	13 (9)	46 (31)	94 (64)	8 (5)	94 (64)	54 (36)	0 (0)	SWOG-8814
Albain (2010)[48.],b	219	210 (96)	30 (14)	74 (34)	136 (62)	9 (4)	133 (61)	86 (39)	219 (100)	
Dowsett (2010)[49.]	306	306 (100)	NR for node-positive patients				243 (79)	63 (21)	0 (0)	TransATAC
Nitz (2017)[50.] Nitz (2019)[51.]	1088	NR for node-positive patients	0 (0)	NR for node-positive patients			1088	0	NR for node-positive patients	WSG PlanB trial
Sestak (2018)[38.]	183	183 (100)	0 (0)	NR			183 (100)	0	0 (0)	TransATAC
EndoPredict										
Filipits (2011)[39.]Filipits (2019)	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)[52.]	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; WSG: West German Study Group, chemo: chemotherapy; ER: estrogen receptor; *HER2*: human epidermal growth factor receptor 2; NR: not reported; SWOG: Southwest Oncology Group.
[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 (2010), but the 60%,10-year disease-free survival in the low-risk group would suggest substantial event rates in patients not receiving adjuvant chemotherapy. The CIs were not reported, but given the small number of low-risk patient intervals, it 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%.[52.] 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	Low-Risk		Intermediate-Risk		High-Risk	
Oncotype DX		*n*	*DFS % (95% CI)*	*n*	*DFS % (95% CI)*	*n*	*DFS % (95% CI)*
Albain (2010)[48.a]	148	55	60 (NR)	46	49 (NR)	47	43 (NR)
		n	*OS % (95% CI)*	*n*	*OS % (95% CI)*	*n*	*OS % (95% CI)*

Study	Total N	Low-Risk		Intermediate-Risk		High-Risk	
Albain (2010)[48.][b]	148	55	77 (NR)	46	68 (NR)	47	51 (NR)
Dowsett (2010)[49.]	296	150	74 (NR)	94	69 (NR)	52	54 (NR)
		n	*DR % (95% CI)*	*n*	*DR % (95% CI)*	*n*	*DR % (95% CI)*
Dowsett (2010)[49.][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)
Filipits (2019) [53.] (EPclin)	536	159	4.4 (0.9 to 7.8)	NA	NA	377	24.2 (19.1 to 29.0)
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)[52.][b] (total)	331	132	7 (2 to 13)	106	15 (9 to 25)	93	25 (17 to 36)
Gnant (2015)[52.][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.

Table 14. Five-Year Results by Risk Categories in Node-Positive Breast Cancer Studies

Study	Total N	Low-Risk		Intermediate-Risk		High-Risk	
Oncotype DX		*n*	*DFS % (95% CI)*	*n*	*DFS % (95% CI)*	*n*	*DFS % (95% CI)*
Nitz (2017)[50.]	1088	110[a]	94.4% (89.5 to 99.3%)	NR		NR	

CI: confidence interval; DFS: disease-free survival; NR: not reported
[a] Includes only patients with 1 positive node

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 for 5 years with tamoxifen alone.[48.] 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 endpoint 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 15). 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 15. Hazard Ratios for Chemotherapy Benefit of Sequential CAF-T vs Tamoxifen Alone by Oncotype DX RS[48.]

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)

Variables	Overall Survival, HR (95% CI)	Disease-Free Survival, HR (95% CI)	
Low RS (<18)		1.34 (0.47 to 3.82)	0.88 (0.38 to 1.92)
Intermediate RS (18-30)		0.95 (0.43 to 2.14)	0.52 (0.20 to 1.52)
High RS (>31)		0.59 (0.32 to 1.11)	0.60 (0.22 to 1.62)

Adapted from Albain et al (2010).[48]
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 [2010]). Overall, there is significant uncertainty in the estimates, and only 1 Simon et al (2009) 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 et al [2009] category B).[49] 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 (RS<18) 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 (2010). Dowsett et al (2010) 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 Plan B trial of *HER*2-negative patients 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 pN0/1 positive node breast cancer and an RS of 11 or less. A total of 2642 patients were included in the trial. The median age was 56 years, 59% were node-negative, 35% were 1 positive node, and 6% were pN2-3. Overall 93% of the patients were HR-positive; the HR positivity was not provided for the node-positive subgroup. 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. Five-year DFS in patients with 1-3 positive nodes or pN1 disease and RS <=11 treated with endocrine therapy alone (n=110) was 94.4% (95% CI, 89.5 to 99.3%). The final analysis of the Plan B trial reported similar results regarding RS scores and DFS.[51]

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 et al (2009) category B studies have suggested uncertainty in the estimates of the distant recurrence-free survival risk for patients in different Oncotype DX RS categories and the RS cutoffs for stratifying into low-, intermediate- and high-risk based on RS have varied across studies. 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 and provided DFS rates for patients with RS <=11 and 1-3 positive nodes or pN1 disease. Although it is expected that the distant recurrence-free survival estimates will be lower than those experienced by patients with node-negative disease, consensus on cutoffs and more certain estimates of risk for patients with 1 to 3 positive nodes 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,[54,55] convincing evidence that decisions based on test results will improve outcomes is lacking, and guidelines do not offer support.[56] The ongoing Clinical Trial Rx for Positive Node, Endocrine Responsive Breast Cancer trial (RxPONDER, NCT01272037) 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. The 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).

The prognostic value of EndoPredict among node-positive patients has been evaluated in 1 prospective study[57] and 2 prospective-retrospective studies.[32,39] As the median follow-up of the prospective study is 41.6 months, it does not meet the BCBSA selection criteria requiring a minimum of 5-year outcomes (Appendix 1) and its findings will not be discussed herein. Authors of the prospective study noted that longer-term follow-up will be available in the near future.

Buus et al (2016) reported on the prognostic value of EndoPredict among node-positive patients from ATAC in the article supplement (Simon et al [2009] 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 et al [2009] 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. Filipits et al (2019) reported results of the longer follow-up of the ABCSG-6 and ABCSG-6 trial samples.[53] The estimates of DR in the Epclin groups were very similar to those reported in the previous publication of this cohort and are shown in Table 13.

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 et al (2009) 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 et al (2009) 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.[58] Patients were selected from consecutive series of breast cancer patients from 2 institutions (Simon et al [2009] category C). No Simon et al (2009) category B studies were identified.

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 et al [2009] 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 genomic risk with MammaPrint.[45] Overall, the study included 942 (14.1%) 1 node, 300 (4.5%) 2 nodes, 154 (2.3%) 3 nodes, and 8 (0.1%) 4+ nodes. In the high clinical risk and low genomic 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). Although the study allowed hormone receptor-negative and *HER2*-positive breast cancer, these patients constituted a small minority (<4%) of the population. Therefore, the 5 year distant recurrence in women with node-positive, hormone receptor-positive, *HER2*-negative breast cancer who did not receive chemotherapy should be similar to the estimate above.

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.

The Simon et al (2009) category A MINDACT study, providing evidence for clinical utility, provided 5-year distant recurrence rates of 4.4% (95% CI, 2.6% to 7.3%) in the no chemotherapy group for the high clinical risk and low genomic risk (Mammaprint) group and the benefit of chemotherapy was small to null in this group. Therefore, 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
One Simon et al (2009) category A study has investigated the use of MammaPrint to assess distant recurrence risk in women with node-positive breast cancer who were classified as high clinical risk based on a modified version of Adjuvant! Online tool. The Simon et al (2009) category A study found 5-year distant recurrence rates for treated and untreated women categorized as low-risk based on MammaPrint are similar. Distant recurrence rates for patients categorized as low-risk based on MammaPrint were 4.4% (95% CI, 2.6% to 7.3%) in the no chemotherapy group. The Simon et al (2009) category A study of MammaPrint has currently provided 5-year distant recurrence outcomes, which have shown that patients identified by MammaPrint as low-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).

Gnant et al (2015) examined the potential prognostic value of the prediction analysis of microarray 50-gene set (PAM50) ROR score, including clinical predictors, among node-positive patients in a combined analysis of the ABCSG-8 and ATAC trial samples.[52] Samples from 543 patients treated with endocrine therapy alone were included, and 10-year distant recurrence (the primary endpoint) 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 et al (2009) category B study (Gnant et al [2015]) meeting inclusion criteria were identified. The 10 year distant recurrence rate in patients with a single positive node and low-risk ROR scores is about two-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 Radiotherapy
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 U.S. 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).

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 16).[59.] This study is Simon et al (2009) 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 the DCIS category are listed in Table 17. 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 16. Characteristics of Retrospective Studies Evaluating the Oncotype DX DCIS Score

Study	Country	Study Population	Design	N	Median FU, y
Solin et al (2013)[59.]	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 17. 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*
Solin et al (2013)[59.]								
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.
[a] Local recurrence of DCIS and invasive carcinoma combined.

The study limitations stated in Tables 18 and 19 are those notable in the current review; this is not a comprehensive gaps assessment.

Table 18. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Solin et al (2013)[59.]			3. No comparator (standard of care is clinical risk indicators)		

The study limitations 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 19. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Solin et al (2013)[59]	2. Sample of women from another study					

The study limitations 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 with 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 Simon et al (2009) category B study provided evidence for clinical validity which showed an invasive breast cancer recurrence rate under the 10% threshold.

Section Summary: Oncotype DX Breast DCIS Score
The evidence consists of 1 Simon et al (2009) category B study. Based on the Oncotype DX Breast DCIS Score of low-risk for recurrence, it is unclear whether estimated recurrence risks for this group are low enough or estimated with sufficient precision, 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 cm or less in size and (2) patients with tumors 2.5 cm or less in size. Conclusions are also limited because there are no comparison recurrence estimates for women based on the 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 needs 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 (AIs) following 5 years of endocrine therapy have reported inconsistent benefits in BCSS and the 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.[60.] 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 clinicopathologic parameters such as tumor size and nodal status to estimate the risk of breast cancer recurrence while deciding on extended endocrine therapy. A clinical tool was developed and validated in 2018 (CTS5).[61.] 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 the number of nodes) that physicians and patients currently use when considering extended endocrine therapy. The 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 21 , to compare with distant recurrence rates calculated using gene expression profiling tests.

Table 20 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 10 years of endocrine therapy.[41,42,62,63,64,65,66,38.] All studies were prospective-retrospective designs of patients with early-stage node-negative or node-positive breast cancer receiving up to 10 years of endocrine therapy. The study by Zhang et al (2013)[42.] examining prognosis and an additional nested case-control study (Sgroi et al [2013])[67.] 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)[42.] included only postmenopausal women. Samples from several studies were used multiple times in analyses for the different molecular assays. Table 21 summarizes distant recurrence rates. Some studies provided results other than distant recurrence rates; those results appear in Tables 22, 23 and 24.

Table 20. Characteristics of Patients in Extended Endocrine Therapy Studies of Prognosis or Predicting Treatment Benefit

Study		Tumor Size, n (%)		Nodes, n (%)			Adjuvant Chemo, n (%)	Trial
	N	*≤2 cm*	*>2 cm*	*None*	*1-3*	*≥4*		
Oncotype DX								
Sestak (2013)[65.]	940			683 (73)	257 (27)		0 (0)	TransATAC
Sestak (2018)[38.]	689			535 (78)	154 (22)		0 (0)	TransATAC
EndoPredict								
Dubsky (2013)[62.,a] Filipits (2019) [53.]	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								

Study		Tumor Size, n (%)		Nodes, n (%)			Adjuvant Chemo, n (%)	Trial
Zhang (2013)[42]	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)[41]	597	442 (74)	155 (26)	597 (100)	0 (0)	0 (0)	0 (0)	TransATAC
Sgroi (2013)[67]	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)[66]	652	499 (77)	145 (22)	652 (100)	0 (0)	0 (0)	0 (0)	Stockholm Trial TAM-treated
Prosigna								
Filipits (2014)[63]	1246	NR (see below)		919 (74)	327 (26)		0 (0)	ABCSG-8
Sestak (2013)[65]	940			683 (73)	257 (27)		0 (0)	TransATAC
Sestak (2015),[64] all patients	862	587 (68)	275 (32)	647 (75)	180 (21)	35 (4)	0 (0)	TransATAC
Sestak (2015),[64] 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)[61]	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 21. Distant Recurrence Rates for Extended Endocrine Therapy Studies

Study			Low-Risk		Intermediate-Risk		High-Risk	
	N	*During Years*	*n*	*DR (95% CI), %*	*n*	*DR (95% CI), %*	*n*	*DR (95% CI), %*
Oncotype DX								
Sestak (2013)[65]	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)[62,a] (EP)	998	5-10	503	3.7 (0.9 to 6.5)		NA	495	9.0 (NR)
Dubsky (2013)[62,a] (EPclin)	998	5-10	642	1.8 (0.1 to 3.5)		NA	356	13.0 (NR)
Filipits (2019)[53] (EPclin); node-negative only	976	5-10	764	2.1 (0.9 to 3.3)		NA	212	5.9 (2.2 to 9.5)
Note: Longer follow-up of cohort from Dubsky (2013)		5-15	764	3.1 (1.5 to 4.8)		NA	212	15.1 (4.0 to 24.9)
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)[42] (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)[42] (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)[41]	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)[63]	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)

Study			Low-Risk		Intermediate-Risk		High-Risk	
Sestak (2013)[65]	940	5-10	NR	4.1 (NR)	NR	NR	NR	NR
Sestak (2015),[64] 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),[64] 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)[61]	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)[66]		*At years*	*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.[65] 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 distant recurrence rate of 4.8% (95% CI, 2.9% to 7.9%) during years 5 to 10 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 one 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 ABCSG-6 and ABCSG-8 trials (see Table 21) treated with 5 years of endocrine therapy (tamoxifen for 5 years or tamoxifen for 2 years followed by anastrozole for 3 years).[62.] 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 the gene EP alone and combined with a score that included the nodal status and tumor size (EPclin). In the EP low-risk group, the cumulative late distant recurrence rate between 5 and 10 years was 3.7% (95% CI, 0.9% to 6.5%) (see Table 21). 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 21). 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. Filipits et al (2019) reported longer follow-up of the cohort from the ABCSG-6 and ABCSG-8 trials.[53.] Overall, 1386 women were distant recurrence-free at 5 years; 976 of these (764 EPclin low, 212 EPclin high) were node-negative. The DR rates are shown in Table 21. The authors also reported a multivariable Cox analysis showing that the EPclin score was a predictor of late recurrence (5- to 15-year period) after adjusting for the CTS5 score in the node-negative cohort.

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 et al [2009] category B) of patients untreated with adjuvant chemotherapy enrolled in the ABCSG-6 and -8 trials. However, in the Filipits et al (2019) study, the lower-bound of the 95% CI for the distant recurrence rate in the high-risk group falls within a range that may be clinically meaningful for decision-making about avoiding extended endocrine treatment both at 5-10 years (5.9%; 95% CI, 2.2% to 9.5%) and at 5-15 years (15.1%; 95% CI, 4.0% to 24.9%). These results suggest the possibility that a proportion of high-risk patients may still have been unnecessarily treated with extended endocrine therapy based on a gene expression profiling result. ROC 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. One of the studies (Sestak et al, 2018) provided evidence for clinical validity with tight precision, which would allow for the identification of women who can safely forgo extended endocrine therapy. The second study (Filipits et al, 2019) also reported a low point estimate for the low-risk group; however, it did not adequately discriminate low-risk from high-risk. This is because the 5-10 year DR rate in the high-risk group was low (5.9%; 95% CI, 2.2% to 9.5%) and its 95% CI overlapped highly with that of the low-risk group (2.1%; 95% CI, 0.9% to 3.3%). Although the DR rate for the high-risk group was higher at 5-15 years (15.1%; 95% CI, 4.0% to 24.9%), as the 95% CI was wide and included the threshold of 10%, it also had insufficient precision to discriminate low-risk from high-risk.

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.[42] Patient samples from 2 studies were used: the STO-3 trial (Simon et al [2009] category B), which compared 2 or 5 years of tamoxifen with no treatment in early-stage breast cancer; and a cohort (Simon et al [2009] 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 STO-3 trial *HER2*-positive, and 10% of the cohort *HER2*-positive. Data from patients in the untreated arm of the STO-3 trial were used for model development; the tamoxifen arm of the trial and the 2-institution cohort were used for validation. The primary endpoint was distant recurrence-free survival (censoring for any cause of death). The STO-3 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 20). 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 STO-3 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.

In 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 et al [2009] category B) not treated with adjuvant chemotherapy.[41] 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 [2013][42.]), 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 2 important decisions in the management of postmenopausal patients with estrogen-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 in the 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 (2017)[68.] calculated distant recurrence-free survival 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 STO-3 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 STO-3 population and the medical center population as low-risk, respectively. Median follow-up was 17 years for the STO-3 study and 10 years for the medical center cohort. Table 22 lists the 5- to 15-year distant recurrence-free survival rates (as categorized by BCI risk) for the 2 trial populations.

Table 22. 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 (2017)[68.]	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.[67.] 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 endpoint; 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 23).
Zhang et al (2013) also reported a larger potential relative risk reduction in the high-risk group of the STO-3 trial, with similar uncertainty reflected in the CIs (see Table 23).[42.]

Table 23. 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)[67.]	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)[42.]	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 of data from women who were node-negative, participating in an RCT of tamoxifen vs no systemic therapy, with over 20 years of follow-up, the STO-3 trial, (see Table 20).[66.] This is a Simon et al (2009) 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 21 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.[69.]

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

Sestak et al (2013) reported limited results concerning late recurrences obtained from patients in the ATAC trial who received anastrozole with tamoxifen alone or in combination.[65.] 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 endpoint (censored at death). The sample included patients with node-positive and node-negative cancers but the proportions were not reported. There were 83 distant recurrences in 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)[64.] combined samples of women with hormone receptor-positive, *HER2*-negative cancers from the ABCSG-8 and TransATAC studies included in the 2 prior publications.[63.65.] 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 24). 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 24), 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.

Table 24. Classification and Reclassification Achieved by Adding ROR Score to the CTS

Distant Recurrence		***CTS***					***CTS***			
		Low	*Int*	*High*	*Total*		*Low*	*Int*	*High*	*Total*
	Low	18	14	0	32		25	3	0	28
ROR	*Intermediate*	7	31	7	45	***ROR + CTS***	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***					***CTS***			
		Low	*Int*	*High*	*Total*		*Low*	*Int*	*High*	*Total*

Distant Recurrence				CTS					CTS	
	Low	837	273	41	1151		1030	136	0	1166
ROR	*Intermediate*	209	221	63	493	***ROR + CTS***	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 (e.g., lack of reporting recurrence rates by ROR categories, lack of CIs) in the studies that evaluated clinical validity preclude any conclusions for the 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 study limitations stated in Tables 25 and 26 are those notable in the current review; this is not a comprehensive gaps assessment.

Table 25. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of FU[e]
Dubsky et al (2013)[62]	4. includes both node-negative and -positive patients			4. Reclassification of diagnostic or risk categories not reported	
Sestak et al (2013)[65]	4. includes both node-negative and -positive patients			4. Reclassification of diagnostic or risk categories not reported	
Sgroi et al (2013)[41]	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)[67]	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)[42]				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)[63]	4. includes both node-negative and -positive patients			4. Reclassification of diagnostic or risk categories not reported	
Esserman et al (2017)[66]	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)[64]	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 study relevance limitations 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 26. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Dubsky et al (2013)[62]	2. Sample of women from another study					
Sestak et al (2013)[65]	2. Sample of women from another study					
Sgroi et al (2013)[41]	2.Sample of women from another study					
Sgroi et al (2013)[67]	2. Sample of women from another study					
Zhang et al (2013)[42]	2. Sample of women from another study					
Filipits et al (2014)[63]	2. Sample of women from another study					
Esserman et al (2017)[66]	2. Sample of women from another study					

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Sestak et al (2018)[38.]	2.Sample of women from another study					

The study limitations 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 with 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 AIs after 5 years of endocrine therapy have reported inconsistent benefits in BCSS and the duration of AI use is uncertain. Recent trials comparing the use of AIs 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.[11.] Despite credible studies, there are conflicting reports and uncertainty concerning AIs. 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 Adjuvant Tamoxifen: Longer Against Shorter trial reported a cumulative risk of endometrial cancer of 3.1% in years 5 to 14 with tamoxifen treatment. The relative risk for pulmonary embolus was 1.9 (95% CI 1.1 to 3.1) in that same follow-up period. AIs have increased cardiovascular and musculoskeletal adverse events compared with tamoxifen.
In addition, noncompliance rates in women taking endocrine therapy are as high as 30%.[70.]

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 clinicopathologic parameters such as tumor size and nodal status to estimate the risk of breast cancer recurrence while deciding on extended endocrine therapy. A clinical tool has been validated (CTS5). The CTS5 is simple to use and incorporates clinical parameters (tumor size, tumor grade, age, and the number of nodes) that physicians and patients currently use when considering extended endocrine therapy. The 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 the 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 consistently improved reclassification of patients to lower risk categories.

Triple-Negative Breast Cancer Considering Neoadjuvant Chemotherapy
Triple-Negative Breast Cancer (TNBC) is a type of cancer that lacks expression of estrogen and progesterone receptors (≤ 1% per immunohistochemistry [IHC]), as well as *HER2* amplification (0 to 1+ by IHC or IHC 2+ and fluorescence in situ hybridization [FISH] negative [not amplified]). TNBC represents approximately 15% to 20% of all breast cancers and tends to be more aggressive than other breast cancer types. Also compared with other breast cancers, patients with TNBC are not candidates for currently available targeted therapies (ie, ER-positive, *HER2*-positive-targeted). Standard-of-care management of TNBC is generally similar to that of other breast cancers, but TNBC tends to confer a less favorable prognosis. However, previous research has suggested that the 20-40% of women with TNB who achieve pathological complete response following neoadjuvant chemotherapy may achieve a similar long-term survival prognosis as patients with non-TNBC breast cancers[5]. This heterogeneity suggests that there may be subtypes of women with TNBC that significantly differ in their likelihood of response to neoadjuvant chemotherapy and differ in their risk: benefit treatment considerations. Thus, classification of women based on TNBC subtype may help clarify their likelihood of net health benefits from neoadjunctive chemotherapy and help guide the decisions to receive treatment.

The Insight TNBCtype uses next-generation sequencing to classify expression data from 101 genes into 5 molecular subtypes including basal-like 1 (BL1), basal-like 2 (BL2), luminal androgen receptor (LAR), mesenchymal stem-like (MSL), and mesenchymal (M), as well as a complementary immunomodulatory (IM) classifier. The stated purpose of the test is to help direct selection and combination of chemotherapies and to support development of novel TNBC targeted therapeutics and diagnostics.

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).

For individuals who have TNBC considering neoadjuvant chemotherapy who receive gene expression profiling with the Insight TNBCtype test, the evidence includes 2 retrospective cohort studies.[71,72] Neither were Simon et al (2009) category B studies. Specimens were selected from public databases treated with neoadjuvant chemotherapy regardless of TNBC status and were not prospectively designed or powered to specifically address the triple-negative breast cancer population or their specific therapeutic questions. The number of tumor-specific TNBC subtypes varied from 4 to 7. The studies were consistent in demonstrating that the basal-like 1 (BL1) subtype had the highest pathological complete response rate after neoadjuvant chemotherapy (range, 41% to 52%). The lowest pathological complete response rates were consistently associated with the basal-like 2 (BL2) (0% to 18%) and luminal androgen receptor (LAR) (10% to 29%) subtypes. However, important study design and conduct limitations preclude drawing conclusions based on these findings.

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.

Two studies provided evidence for the clinical validity of the Insight TNBCtype test for patients with triple-negative breast cancer. Although findings from these studies suggest that TNBC subtypes may differ in response to neoadjuvant chemotherapy, these results are very likely due to chance as the studies were not prospectively designed or powered to specifically address the triple-negative breast cancer population or their specific therapeutic questions. Additional Simon et al (2009) category A or B studies are required.

Section Summary: Insight TNBCtype Test
Studies identified that evaluated clinical validity of the Insight TNBCtype test for patients with triple-negative breast cancer did not meet Simon et al (2009) category B criteria. Although findings from available studies suggest that TNBC subtypes may differ in response to neoadjuvant chemotherapy, important study design and conduct limitations preclude drawing conclusions based on these findings. Additional Simon et al (2009) category A or B studies are required.

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

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.[73] 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.[41] 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)[74] examined cross-stratification between the BCI and Oncotype DX RS using the same data as Sgroi et al (2013).[41] 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 breast cancer algorithm.[46] 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 immunohistochemical 4 was similar.

Hornberger et al (2012) conducted a systematic review of the clinical validity, clinical utility, change in clinical practice, and economic implications of early-stage breast cancer stratifiers.[75] 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.[76] 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.[77] 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.[78] 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).[79]

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,[80] 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 are 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 r=0.91) than for estrogen receptor status (Spearman r=0.65), but worse concordance (at various cut points) for progesterone receptor status (99%) than for estrogen receptor status (88%).[81]

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.[82] Most patients had estrogen receptor-positive, *HER2*-negative disease; approximately half of the 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.[83] 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

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 human epidermal growth factor receptor 2 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% confidence interval [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 the patients in these studies were classified as low-risk. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Breast Cancer Index

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the Breast Cancer Index, the evidence includes findings from 2 prospective-retrospective studies and a registry-based observational study. The findings from the 2 prospective-retrospective studies showed that a low-risk Breast Cancer Index score is associated with low 10-year distant recurrence rates (average risk at 10 years, 5%-7%; upper bound of the 95% CI, 8% to 10%). The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

MammaPrint (70-Gene Signature)

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with MammaPrint (70-gene signature), the evidence includes a prospective-retrospective study and a randomized controlled trial 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%). The randomized controlled trial Microarray In Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy 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 (1 to 3 Nodes) Invasive Breast Cancer
For decisions on the management of early-stage node-positive disease, Oncotype DX, EndoPredict, MammaPrint, and Prosigna were evaluated. Only studies presenting a minimum of 5 year distant recurrence rates or 5 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 3 prospective-retrospective studies. The prospective-retrospective studies showed that Oncotype DX stratifies node-positive patients into high- and low-risk for distant recurrence-free survival. The studies have proposed different cutoffs for low-risk. One of the studies with a recurrence score cutoff for low-risk of 18 reported CIs for estimates and those are very wide. The analysis from the Plan B 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 (recurrence score <=11) experienced higher rates of survival than patients classified as high-risk, though no rates were provided. Five-year DFS in patients with 1-3 positive nodes or pN1 disease and recurrence score <=11 treated with endocrine therapy alone (n=110) was 94.4% (95% CI, 89.5 to 99.3%). There is a wide range of survival improvements over which individual patients would elect or refuse adjuvant chemotherapy but consensus on cutoffs and 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 EndoPredict score patients was estimated to be 5% (95% CI, 1% to 9%). In the other study, the 10-year distant recurrence rate in low-risk EndoPredict 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 the 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. The randomized controlled trial

Microarray In Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy showed 5-year distance recurrence rates below the 10% threshold among node-positive (1 to 3 nodes) 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-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with the Prosigna risk of recurrence (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 the 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, Breast Cancer Index, MammaPrint, and Prosigna were evaluated. Studies retrospectively collecting tumor samples from prospective trials that provided 10 year distant recurrence rates or 10 year survival rates were included in this part of the evidence review. Studies comparing genetic assays with clinical risk prediction tools were also included.

Oncotype DX (21-Gene Assay)
For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending endocrine treatment who receive gene expression profiling with Oncotype DX (21-gene assay), the evidence includes 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. However, in 1 of the analyses, the lower-bound of the 95% CI for the distant recurrence rate in the high-risk group falls within a range that may be clinically meaningful for decision-making about avoiding extended endocrine

treatment both at 5-10 years (5.9%; 95% CI, 2.2% to 9.5%) and at 5-15 years (15.1%; 95% CI, 4.0% to 24.9%). The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported although 1 publication reported that EPclin was prognostic after controlling for a clinical prediction tool. Additional prospective trials or retrospective-prospective studies of archived samples are needed to confirm risk of disease recurrence with sufficient precision in both low- and high-risk groups. More importantly, clarity is needed about how the test would inform clinical practice. The evidence is insufficient to determine the effects of the technology on health outcomes.

Breast Cancer Index
For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending tamoxifen treatment who receive gene expression profiling with the Breast Cancer Index, the evidence includes 3 analyses of archived tissue samples from 2 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.

Triple-Negative Breast Cancer
The Insight TNBCtype Test is the only assay investigated for patients with TNBC.

Insight TNBCtype Test
For individuals who have TNBC considering neoadjuvant chemotherapy who receive gene expression profiling with the Insight TNBCtype test, the evidence includes retrospective cohort studies. Although the studies have shown that TNBC subtypes may differ in their response to neoadjuvant chemotherapy, as the studies were not prospectively designed or powered to specifically address the TNBC population or their specific therapeutic questions, conclusions cannot be drawn based on these findings. Additional Simon et al (2009) category A or B studies are required. Additionally, further clarity about how the test would inform clinical practice is still needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

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

Practice Guidelines and Position Statements
National Comprehensive Cancer Network

Adjuvant Chemotherapy for Node-Negative Breast Cancer
Current guidelines from the NCCN for breast cancer (v.6.2020)[2.] provide a summary table assessing multigene assays to inform the addition of adjuvant systemic chemotherapy to adjuvant endocrine therapy (page BINV-N). 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 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 greater 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.6.2020)[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 MammaPrint for this population is 1 and the level of evidence and consensus for Oncotype DX and EndoPredict for this population is 2A. In addition to the summary table, the following recommendation appears in an updated algorithm:

- "Consider gene expression 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 gene expression assays in women with 4 or more ipsilateral axillary lymph nodes. Decisions to administer adjuvant chemotherapy for these groups should be based on clinical factors." For N1mi and N1, "gene expression 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."

Extended Endocrine Therapy
The latest NCCN guideline (v.6.2020) provides a flow chart on adjuvant endocrine therapy (aromatase inhibitors [AI] or tamoxifen) recommendations and considerations, based on menopausal status at diagnosis and after 5 years of therapy, and on prior therapy history (page BINV-K).[2.] The following Table 27 summarizes the contents of the flow chart:

Table 27. NCCN Recommendations and Considerations for Extended Endocrine Therapy

Menopausal Status at Diagnosis	Therapy History	Current Menopausal Status	Recommendations or Considerations
Premenopausal	• Tamoxifen 5 years (category 1) • AI 5 years (category 1)	Postmenopausal	• Recommend AI 5 more years (category 1) • Consider tamoxifen 5 more years
Premenopausal	• Tamoxifen 5 years (category 1) • AI 5 years (category 1)	Premenopausal	• Consider tamoxifen 5 years • No further endocrine therapy
Postmenopausal	AI 5 years (category 1)	Postmenopausal	Consider AI for an additional 3-5 more years
Postmenopausal	AI 2 to 3 years (category 1)	Postmenopausal	Recommend tamoxifen to complete 5 years (category 1)
Postmenopausal	Tamoxifen 2 to 3 years	Postmenopausal	• Recommend AI to complete 5 years (category 1) • Recommend up to 5 years of AI (category 2B)
Postmenopausal	Tamoxifen 4.5 to 6 years	Postmenopausal	• Recommend AI 5 more years (category 1) • Consider tamoxifen to complete 10 years
Postmenopausal	No AI therapy (contraindicated or declined)	Postmenopausal	• Recommend tamoxifen 5 years (category 1) • Consider tamoxifen up to 10 years

AI: aromatase inhibitor; NCCN: National Comprehensive Cancer Network.

American Society of Clinical Oncology

The American Society of Clinical Oncology (ASCO) (2017) 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.[84] and published a focused update of those guidelines in 2019[85]. The ASCO also updated endorsement of the Cancer Care Ontario recommendations on the Role of Patient and Disease Factors in Adjuvant Systemic Therapy Decision Making for Early-Stage, Operable Breast Cancer in 2019. The recommendations are consistent with the table below.[86] Table 28 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 28. Guidelines for Estrogen and Progesterone Receptor-Positive and *HER2*-Negative Breast Cancer and Triple-Negative Breast Cancer

Test	Recommendation	QOE	SOR
Node-negative			
Oncotype DX	"For patients older than 50 years and whose tumors have Oncotype DX recurrence scores of less than 26, and for patients age 50 years or younger whose tumors have Oncotype DX recurrence scores of less than 16, there is little to no benefit from chemotherapy. Clinicians may offer endocrine therapy alone."	High	Strong
	"For patients age 50 years or younger with Oncotype DX recurrence scores of 16 to 25, clinicians may offer chemoendocrine therapy"	Intermediate	Moderate
	"Patients with Oncotype DX recurrence scores of greater than 30 should be considered candidates for chemoendocrine therapy"	High	Strong
	"..oncologists may offer chemoendocrine therapy to patients with Oncotype DX scores of 26 to 30"	Insufficient	Moderate
EndoPredict	Clinician may use the 12-gene risk score to guide decisions on adjuvant systemic chemotherapy	Intermediate	Moderate

Test	Recommendation	QOE	SOR
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
Triple-negative breast cancer			
EndoPredict	If a patient has triple-negative breast cancer, the clinician should not use the 12-gene risk score (EndoPredict) to guide decisions for adjuvant systemic therapy.	Insufficient	Strong
Breast Cancer Index	If a patient has triple-negative breast cancer, the clinician should not use the Breast Cancer Index to guide decisions about adjuvant systemic therapy.	Insufficient	Strong
Oncotype DX	If a patient has triple-negative breast cancer, the clinician should not use the 21-gene RS (Oncotype DX) to guide decisions for adjuvant systemic therapy.	Insufficient	Strong

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

ASCO also has guidelines on adjuvant endocrine therapy. In 2018, ASCO updated its guidelines from 2014[3,4,] on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer.[87,] The update included a qualifying statement that none of the studies used to develop the recommendations showed improvements in overall survival (OS) with extended therapy, and that the recommendations are based on benefits that include prevention of distant recurrence and prevention of second breast cancers. Therefore, the decision to receive extended therapy should involve the weighing of recurrence risk against potential therapy risks and side effects. Recommendations based on nodal status are as follows:

- "Many women with node-negative breast cancer are potential candidates for and may be offered extended AI therapy for up to a total of 10 years of adjuvant endocrine therapy based on considerations of recurrence risk using established prognostic factors. However, as recurrence risk is lower, the benefits are likely narrower for such patients. Women with low-risk node-negative tumors should not routinely be offered extended therapy.
- Women with node-positive breast cancer should be offered extended AI therapy for up to a total of 10 years of adjuvant endocrine therapy."

St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer
In 2017, an international expert Panel, including members from the U.S., 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 29 summarizes relevant recommendations.

Table 29. 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.[88,]

Breast Cancer Group	Recommendation
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."[88]
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."[88]

In 2019, the 16th St. Gallen International Breast Cancer Conference again reviewed current evidence on locoregional and systemic therapies for early breast cancer.[89] Statements related to use of genomic assays included the following:

- "The Panel believed strongly that genomic assays are valuable for determining whether or not to recommend adjuvant chemotherapy in T1/T2 N0 ER-positive breast cancers, and recognized the value of such tests in patients with ER-positive tumors and limited nodal involvement."
- "The Panel strongly endorsed the value of genomic assays for determining whether to recommend chemotherapy in T1/T2 N0 tumors, T3 N0 tumors, and TxN1 (1 to 3 positive LN)."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

Ongoing and Unpublished Clinical Trials

Current ongoing and unpublished trials that might influence this review are listed in Table 30.

Table 30. 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	10,273	Sep 2030
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 Common Clinical-Pathological Criteria in Selecting Patients for Adjuvant Chemotherapy in Breast Cancer With 0 to 3 Positive Nodes	6600	Jun 2022
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
NCT02889874	A Randomised Phase III Trial of Adjuvant Radiation Therapy Versus Observation Following Breast Conserving Surgery and Endocrine Therapy in Patients With Molecularly Characterised Luminal A Early Breast Cancer	1167	Dec 2023
NCT02400190	The IDEA Study (Individualized Decisions for Endocrine Therapy Alone)	202	Mar 2026

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03503799	Prospective Assessment of Disease Progression in Primary Breast Cancer Patients Undergoing EndoPredict Gene Expression Testing - a Care Research Study	1200	May 2031
NCT01805271	Randomized, Double-Blind, Multicentric Phase III Trial Evaluating the Safety and Benefit of Adding Everolimus to Adjuvant Hormone Therapy in Women With High Risk of Relapse, ER+ and HER2- Primary Breast Cancer Who Remain Free of Disease After Receiving at Least 1 Year of Adjuvant Hormone Therapy	1279	Apr 2025
ISRCTN42400492	Optimal personalised treatment of early breast cancer using multiparameter analysis (OPTIMA)	4500	Dec 2031
NCT03904173	Establishment of Molecular Profiling for Individual Clinical Routine Treatment Decision in Early Breast Cancer	2150	Dec 2043

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.
[b] ISRCTN registry

Appendix 1

1. Study Selection Criteria by Specific Indications

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

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

BCBSA excluded studies in which the gene expression algorithm was being developed ("training sets"), studies using convenience samples of patients, and observational studies based on registry data.[22,]. BCBSA also excluded studies in different populations and for different outcomes that may contribute to the body of evidence for the capability of the tests to improve the prediction of prognosis.

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

For studies evaluating prognosis, BCBSA requires that a minimum of 5-year outcomes (distant disease recurrence, disease-free survival, or overall survival) be presented in node-positive, estrogen receptor-positive patients untreated with adjuvant chemotherapy. In addition, any studies specifically prospectively designed to evaluate the clinical utility of genetic expression profiles with reported 5-year outcomes were included. BCBSA excluded studies in which the gene expression algorithm was being developed ("training sets"), studies using convenience samples of patients, and observational studies based on registry data.[22,]

Ductal Carcinoma In Situ: Radiotherapy Decisions

For studies evaluating prognosis, BCBSA requires that a minimum of 5-year outcomes (distant disease recurrence, disease-free survival, or overall survival) be presented in DCIS patients considering radiotherapy decisions. In addition, any studies specifically prospectively designed to evaluate the clinical utility of genetic expression profiles with reported 5-year outcomes were included. BCBSA excluded studies in which the gene expression algorithm was being developed ("training sets"), studies using convenience samples of patients, and observational studies based on registry data.[22,]

Extended Endocrine Therapy Decisions
For studies evaluating prognosis, BCBSA required that late (ten years or beyond) recurrences (distant disease recurrence, disease-free survival, or overall survival) be presented in estrogen receptor-positive patients. BCBSA excluded studies in which the gene expression algorithm was being developed ("training sets") studies using convenience samples of patients, and observational studies based on registry data.[22,]

Triple-Negative Breast Cancer: Neoadjuvant Chemotherapy Decisions
For studies evaluating prognosis, BCBSA requires that a minimum of 5-year outcomes (distant disease recurrence, disease-free survival, or overall survival) be presented in triple-negative breast cancer patients following neoadjuvant chemotherapy. In addition, any studies specifically prospectively designed to evaluate the clinical utility of genetic expression profiles with reported 5-year outcomes were included. BCBSA excluded studies in which the gene expression algorithm was being developed ("training sets"), studies using convenience samples of patients, and observational studies based on registry data.[22,]

References

1. Colleoni M, Sun Z, Price KN, et al. Annual Hazard Rates of Recurrence for Breast Cancer During 24 Years of Follow-Up: Results From the International Breast Cancer Study Group Trials I to V. J Clin Oncol. Mar 20 2016; 34(9): 927-35. PMID 26786933
2. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 6.2020. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed September 24, 2020.
3. Burstein HJ, Prestrud AA, Seidenfeld J, et al. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. J Clin Oncol. Aug 10 2010; 28(23): 3784-96. PMID 20625130
4. Burstein HJ, Temin S, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: american society of clinical oncology clinical practice guideline focused update. J Clin Oncol. Jul 20 2014; 32(21): 2255-69. PMID 24868023
5. Liedtke C, Mazouni C, Hess KR, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol. Mar 10 2008; 26(8): 1275-81. PMID 18250347
6. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol. Nov 01 2013; 31(31): 3997-4013. PMID 24101045
7. Davies C, Godwin J, Gray R, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet. Aug 27 2011; 378(9793): 771-84. PMID 21802721
8. Tormey DC, Gray R, Falkson HC. Postchemotherapy adjuvant tamoxifen therapy beyond five years in patients with lymph node-positive breast cancer. Eastern Cooperative Oncology Group. J Natl Cancer Inst. Dec 18 1996; 88(24): 1828-33. PMID 8961972
9. Fisher B, Dignam J, Bryant J, et al. Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. J Natl Cancer Inst. May 02 2001; 93(9): 684-90. PMID 11333290
10. Stewart HJ, Prescott RJ, Forrest AP. Scottish adjuvant tamoxifen trial: a randomized study updated to 15 years. J Natl Cancer Inst. Mar 21 2001; 93(6): 456-62. PMID 11259471
11. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet. Mar 09 2013; 381(9869): 805-16. PMID 23219286

12. Gray RG, Rea D, Handley K, et al. aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer [abstract]. J Clin Oncol. 2013;31(18 Suppl):5-5.
13. Jakesz R, Greil R, Gnant M, et al. Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a. J Natl Cancer Inst. Dec 19 2007; 99(24): 1845-53. PMID 18073378
14. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med. Nov 06 2003; 349(19): 1793-802. PMID 14551341
15. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst. Sep 07 2005; 97(17): 1262-71. PMID 16145047
16. Mamounas EP, Jeong JH, Wickerham DL, et al. Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical Adjuvant Breast And Bowel Project B-33 trial. J Clin Oncol. Apr 20 2008; 26(12): 1965-71. PMID 18332472
17. Tjan-Heijnen VCG, van Hellemond IEG, Peer PGM, et al. Extended adjuvant aromatase inhibition after sequential endocrine therapy (DATA): a randomised, phase 3 trial. Lancet Oncol. Nov 2017; 18(11): 1502-1511. PMID 29031778
18. Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E, et al. Optimal Duration of Extended Adjuvant Endocrine Therapy for Early Breast Cancer; Results of the IDEAL Trial (BOOG 2006-05). J Natl Cancer Inst. Jan 01 2018; 110(1). PMID 28922787
19. Khosrow-Khavar F, Filion KB, Al-Qurashi S, et al. Cardiotoxicity of aromatase inhibitors and tamoxifen in postmenopausal women with breast cancer: a systematic review and meta-analysis of randomized controlled trials. Ann Oncol. Mar 01 2017; 28(3): 487-496. PMID 27998966
20. Amir E, Seruga B, Niraula S, et al. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. J Natl Cancer Inst. Sep 07 2011; 103(17): 1299-309. PMID 21743022
21. Tseng OL, Spinelli JJ, Gotay CC, et al. Aromatase inhibitors are associated with a higher fracture risk than tamoxifen: a systematic review and meta-analysis. Ther Adv Musculoskelet Dis. Apr 2018; 10(4): 71-90. PMID 29619093
22. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst. Nov 04 2009; 101(21): 1446-52. PMID 19815849
23. Kelly CM, Krishnamurthy S, Bianchini G, et al. Utility of oncotype DX risk estimates in clinically intermediate risk hormone receptor-positive, HER2-normal, grade II, lymph node-negative breast cancers. Cancer. Nov 15 2010; 116(22): 5161-7. PMID 20665886
24. Peto R, Davies C, Godwin J, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet. Feb 04 2012; 379(9814): 432-44. PMID 22152853
25. Pauker SG, Kassirer JP. Therapeutic decision making: a cost-benefit analysis. N Engl J Med. Jul 31 1975; 293(5): 229-34. PMID 1143303
26. Pauker SG, Kassirer JP. The threshold approach to clinical decision making. N Engl J Med. May 15 1980; 302(20): 1109-17. PMID 7366635
27. Simes RJ, Coates AS. Patient preferences for adjuvant chemotherapy of early breast cancer: how much benefit is needed?. J Natl Cancer Inst Monogr. 2001; (30): 146-52. PMID 11773309
28. Duric VM, Stockler MR, Heritier S, et al. Patients' preferences for adjuvant chemotherapy in early breast cancer: what makes AC and CMF worthwhile now?. Ann Oncol. Nov 2005; 16(11): 1786-94. PMID 16126738
29. Thewes B, Meiser B, Duric VM, et al. What survival benefits do premenopausal patients with early breast cancer need to make endocrine therapy worthwhile?. Lancet Oncol. Aug 2005; 6(8): 581-8. PMID 16054569
30. Henderson IC. Breast cancer: fundamentals of evidence-based disease management. New York: Oxford University Press; 2015.

31. Hamelinck VC, Bastiaannet E, Pieterse AH, et al. A Prospective Comparison of Younger and Older Patients' Preferences for Adjuvant Chemotherapy and Hormonal Therapy in Early Breast Cancer. Clin Breast Cancer. Oct 2016; 16(5): 379-388. PMID 27212474
32. Buus R, Sestak I, Kronenwett R, et al. Comparison of EndoPredict and EPclin With Oncotype DX Recurrence Score for Prediction of Risk of Distant Recurrence After Endocrine Therapy. J Natl Cancer Inst. Nov 2016; 108(11). PMID 27400969
33. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med. Dec 30 2004; 351(27): 2817-26. PMID 15591335
34. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol. Aug 10 2006; 24(23): 3726-34. PMID 16720680
35. Tang G, Shak S, Paik S, et al. Comparison of the prognostic and predictive utilities of the 21-gene Recurrence Score assay and Adjuvant! for women with node-negative, ER-positive breast cancer: results from NSABP B-14 and NSABP B-20. Breast Cancer Res Treat. May 2011; 127(1): 133-42. PMID 21221771
36. Sparano JA, Gray RJ, Makower DF, et al. Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. Nov 19 2015; 373(21): 2005-14. PMID 26412349
37. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. Jul 12 2018; 379(2): 111-121. PMID 29860917
38. Sestak I, Buus R, Cuzick J, et al. Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor-Positive Breast Cancer: A Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol. Apr 01 2018; 4(4): 545-553. PMID 29450494
39. Filipits M, Rudas M, Jakesz R, et al. A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. Clin Cancer Res. Sep 15 2011; 17(18): 6012-20. PMID 21807638
40. Sestak I, Martin M, Dubsky P, et al. Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone. Breast Cancer Res Treat. Jul 2019; 176(2): 377-386. PMID 31041683
41. Sgroi DC, Sestak I, Cuzick J, et al. Prediction of late distant recurrence in patients with oestrogen-receptor-positive breast cancer: a prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population. Lancet Oncol. Oct 2013; 14(11): 1067-1076. PMID 24035531
42. Zhang Y, Schnabel CA, Schroeder BE, et al. Breast cancer index identifies early-stage estrogen receptor-positive breast cancer patients at risk for early- and late-distant recurrence. Clin Cancer Res. Aug 01 2013; 19(15): 4196-205. PMID 23757354
43. Bueno-de-Mesquita JM, Sonke GS, van de Vijver MJ, et al. Additional value and potential use of the 70-gene prognosis signature in node-negative breast cancer in daily clinical practice. Ann Oncol. Sep 2011; 22(9): 2021-2030. PMID 19955335
44. van 't Veer LJ, Yau C, Yu NY, et al. Tamoxifen therapy benefit for patients with 70-gene signature high and low risk. Breast Cancer Res Treat. Nov 2017; 166(2): 593-601. PMID 28776283
45. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med. Aug 25 2016; 375(8): 717-29. PMID 27557300
46. Dowsett M, Sestak I, Lopez-Knowles E, et al. Comparison of PAM50 risk of recurrence score with oncotype DX and IHC4 for predicting risk of distant recurrence after endocrine therapy. J Clin Oncol. Aug 01 2013; 31(22): 2783-90. PMID 23816962
47. Gnant M, Filipits M, Greil R, et al. Predicting distant recurrence in receptor-positive breast cancer patients with limited clinicopathological risk: using the PAM50 Risk of Recurrence score in 1478 postmenopausal patients of the ABCSG-8 trial treated with adjuvant endocrine therapy alone. Ann Oncol. Feb 2014; 25(2): 339-45. PMID 24347518
48. Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-

receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Lancet Oncol. Jan 2010; 11(1): 55-65. PMID 20005174
49. Dowsett M, Cuzick J, Wale C, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. J Clin Oncol. Apr 10 2010; 28(11): 1829-34. PMID 20212256
50. Nitz U, Gluz O, Christgen M, et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial. Breast Cancer Res Treat. Oct 2017; 165(3): 573-583. PMID 28664507
51. Nitz U, Gluz O, Clemens M, et al. West German Study PlanB Trial: Adjuvant Four Cycles of Epirubicin and Cyclophosphamide Plus Docetaxel Versus Six Cycles of Docetaxel and Cyclophosphamide in HER2-Negative Early Breast Cancer. J Clin Oncol. Apr 01 2019; 37(10): 799-808. PMID 30785826
52. Gnant M, Sestak I, Filipits M, et al. Identifying clinically relevant prognostic subgroups of postmenopausal women with node-positive hormone receptor-positive early-stage breast cancer treated with endocrine therapy: a combined analysis of ABCSG-8 and ATAC using the PAM50 risk of recurrence score and intrinsic subtype. Ann Oncol. Aug 2015; 26(8): 1685-91. PMID 25935792
53. Filipits M, Dubsky P, Rudas M, et al. Prediction of Distant Recurrence Using EndoPredict Among Women with ER + , HER2 - Node-Positive and Node-Negative Breast Cancer Treated with Endocrine Therapy Only. Clin Cancer Res. Jul 01 2019; 25(13): 3865-3872. PMID 31064782
54. Jasem J, Fisher CM, Amini A, et al. The 21-Gene Recurrence Score Assay for Node-Positive, Early-Stage Breast Cancer and Impact of RxPONDER Trial on Chemotherapy Decision-Making: Have Clinicians Already Decided?. J Natl Compr Canc Netw. Apr 2017; 15(4): 494-503. PMID 28404760
55. Roberts MC, Miller DP, Shak S, et al. Breast cancer-specific survival in patients with lymph node-positive hormone receptor-positive invasive breast cancer and Oncotype DX Recurrence Score results in the SEER database. Breast Cancer Res Treat. Jun 2017; 163(2): 303-310. PMID 28243896
56. Harris LN, Ismaila N, McShane LM, et al. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. Apr 01 2016; 34(10): 1134-50. PMID 26858339
57. Ettl J, Anders SI, Hapfelmeier A, et al. First prospective outcome data for the second-generation multigene test Endopredict in ER-positive/HER2-negative breast cancer. Arch Gynecol Obstet. Dec 2020; 302(6): 1461-1467. PMID 32902674
58. Mook S, Schmidt MK, Viale G, et al. The 70-gene prognosis-signature predicts disease outcome in breast cancer patients with 1-3 positive lymph nodes in an independent validation study. Breast Cancer Res Treat. Jul 2009; 116(2): 295-302. PMID 18661261
59. Solin LJ, Gray R, Baehner FL, et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. J Natl Cancer Inst. May 15 2013; 105(10): 701-10. PMID 23641039
60. Esserman L, Gallant E, Alvarado M. Less Is More: The Evolving Surgical Approach to Breast Cancer. Am Soc Clin Oncol Educ Book. 2016; 35: e5-e10. PMID 27249759
61. Dowsett M, Sestak I, Regan MM, et al. Integration of Clinical Variables for the Prediction of Late Distant Recurrence in Patients With Estrogen Receptor-Positive Breast Cancer Treated With 5 Years of Endocrine Therapy: CTS5. J Clin Oncol. Jul 01 2018; 36(19): 1941-1948. PMID 29676944
62. Dubsky P, Brase JC, Jakesz R, et al. The EndoPredict score provides prognostic information on late distant metastases in ER+/HER2- breast cancer patients. Br J Cancer. Dec 10 2013; 109(12): 2959-64. PMID 24157828
63. Filipits M, Nielsen TO, Rudas M, et al. The PAM50 risk-of-recurrence score predicts risk for late distant recurrence after endocrine therapy in postmenopausal women with

endocrine-responsive early breast cancer. Clin Cancer Res. Mar 01 2014; 20(5): 1298-305. PMID 24520097
64. Sestak I, Cuzick J, Dowsett M, et al. Prediction of late distant recurrence after 5 years of endocrine treatment: a combined analysis of patients from the Austrian breast and colorectal cancer study group 8 and arimidex, tamoxifen alone or in combination randomized trials using the PAM50 risk of recurrence score. J Clin Oncol. Mar 10 2015; 33(8): 916-22. PMID 25332252
65. Sestak I, Dowsett M, Zabaglo L, et al. Factors predicting late recurrence for estrogen receptor-positive breast cancer. J Natl Cancer Inst. Oct 02 2013; 105(19): 1504-11. PMID 24029245
66. Esserman LJ, Yau C, Thompson CK, et al. Use of Molecular Tools to Identify Patients With Indolent Breast Cancers With Ultralow Risk Over 2 Decades. JAMA Oncol. Nov 01 2017; 3(11): 1503-1510. PMID 28662222
67. Sgroi DC, Carney E, Zarrella E, et al. Prediction of late disease recurrence and extended adjuvant letrozole benefit by the HOXB13/IL17BR biomarker. J Natl Cancer Inst. Jul 17 2013; 105(14): 1036-42. PMID 23812955
68. Schroeder B, Zhang Y, Stal O, et al. Risk stratification with Breast Cancer Index for late distant recurrence in patients with clinically low-risk (T1N0) estrogen receptor-positive breast cancer. NPJ Breast Cancer. 2017; 3: 28. PMID 28795152
69. Delahaye LJMJ, Drukker CA, Dreezen C, et al. A breast cancer gene signature for indolent disease. Breast Cancer Res Treat. Jul 2017; 164(2): 461-466. PMID 28451965
70. Burstein HJ, Griggs JJ, Prestrud AA, et al. American society of clinical oncology clinical practice guideline update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. J Oncol Pract. Sep 2010; 6(5): 243-6. PMID 21197188
71. Lehmann BD, Jovanovic B, Chen X, et al. Refinement of Triple-Negative Breast Cancer Molecular Subtypes: Implications for Neoadjuvant Chemotherapy Selection. PLoS One. 2016; 11(6): e0157368. PMID 27310713
72. Masuda H, Baggerly KA, Wang Y, et al. Differential response to neoadjuvant chemotherapy among 7 triple-negative breast cancer molecular subtypes. Clin Cancer Res. Oct 01 2013; 19(19): 5533-40. PMID 23948975
73. Bosl A, Spitzmuller A, Jasarevic Z, et al. MammaPrint versus EndoPredict: Poor correlation in disease recurrence risk classification of hormone receptor positive breast cancer. PLoS One. 2017; 12(8): e0183458. PMID 28850621
74. Sestak I, Zhang Y, Schroeder BE, et al. Cross-Stratification and Differential Risk by Breast Cancer Index and Recurrence Score in Women with Hormone Receptor-Positive Lymph Node-Negative Early-Stage Breast Cancer. Clin Cancer Res. Oct 15 2016; 22(20): 5043-5048. PMID 27252417
75. Hornberger J, Alvarado MD, Rebecca C, et al. Clinical validity/utility, change in practice patterns, and economic implications of risk stratifiers to predict outcomes for early-stage breast cancer: a systematic review. J Natl Cancer Inst. Jul 18 2012; 104(14): 1068-79. PMID 22767204
76. Fan C, Oh DS, Wessels L, et al. Concordance among gene-expression-based predictors for breast cancer. N Engl J Med. Aug 10 2006; 355(6): 560-9. PMID 16899776
77. Espinosa E, Vara JA, Redondo A, et al. Breast cancer prognosis determined by gene expression profiling: a quantitative reverse transcriptase polymerase chain reaction study. J Clin Oncol. Oct 10 2005; 23(29): 7278-85. PMID 16129846
78. Kelly CM, Bernard PS, Krishnamurthy S, et al. Agreement in risk prediction between the 21-gene recurrence score assay (Oncotype DX(R)) and the PAM50 breast cancer intrinsic Classifier in early-stage estrogen receptor-positive breast cancer. Oncologist. 2012; 17(4): 492-8. PMID 22418568
79. Prat A, Parker JS, Fan C, et al. Concordance among gene expression-based predictors for ER-positive breast cancer treated with adjuvant tamoxifen. Ann Oncol. Nov 2012; 23(11): 2866-2873. PMID 22532584
80. Badve SS, Baehner FL, Gray RP, et al. Estrogen- and progesterone-receptor status in ECOG 2197: comparison of immunohistochemistry by local and central laboratories and

quantitative reverse transcription polymerase chain reaction by central laboratory. J Clin Oncol. May 20 2008; 26(15): 2473-81. PMID 18487567
81. Khoury T, Yan L, Liu S, et al. Oncotype DX RT-qPCR assay for ER and PR correlation with IHC: a study of 3 different clones. Appl Immunohistochem Mol Morphol. Mar 2015; 23(3): 178-87. PMID 24992175
82. Drukker CA, Elias SG, Nijenhuis MV, et al. Gene expression profiling to predict the risk of locoregional recurrence in breast cancer: a pooled analysis. Breast Cancer Res Treat. Dec 2014; 148(3): 599-613. PMID 25414025
83. Fitzal F, Filipits M, Rudas M, et al. The genomic expression test EndoPredict is a prognostic tool for identifying risk of local recurrence in postmenopausal endocrine receptor-positive, her2neu-negative breast cancer patients randomised within the prospective ABCSG 8 trial. Br J Cancer. Apr 14 2015; 112(8): 1405-10. PMID 25867274
84. Krop I, Ismaila N, Stearns V. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Focused Update Guideline Summary. J Oncol Pract. Nov 2017; 13(11): 763-766. PMID 28696818
85. Andre F, Ismaila N, Henry NL, et al. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: ASCO Clinical Practice Guideline Update-Integration of Results From TAILORx. J Clin Oncol. Aug 01 2019; 37(22): 1956-1964. PMID 31150316
86. Henry NL, Somerfield MR, Abramson VG, et al. Role of Patient and Disease Factors in Adjuvant Systemic Therapy Decision Making for Early-Stage, Operable Breast Cancer: Update of the ASCO Endorsement of the Cancer Care Ontario Guideline. J Clin Oncol. Aug 01 2019; 37(22): 1965-1977. PMID 31206315
87. Burstein HJ, Lacchetti C, Anderson H, et al. Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer: ASCO Clinical Practice Guideline Focused Update. J Clin Oncol. Feb 10 2019; 37(5): 423-438. PMID 30452337
88. Curigliano G, Burstein HJ, Winer EP, et al. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. Ann Oncol. Aug 01 2017; 28(8): 1700-1712. PMID 28838210
89. Burstein HJ, Curigliano G, Loibl S, et al. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. Ann Oncol. Oct 01 2019; 30(10): 1541-1557. PMID 31373601
90. Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 2.04.36 (November 2020).

Documentation for Clinical Review

Please provide the following documentation:

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

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

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

Type	Code	Description
CPT®	0045U	Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score
	0153U	Oncology (breast), mRNA, gene expression profiling by next-generation sequencing of 101 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a triple negative breast cancer clinical subtype(s) with information on immune cell involvement
	81479	Unlisted molecular pathology procedure
	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 reported 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
	81522	Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score
	81599	Unlisted multianalyte assay with algorithmic analysis
HCPCS	S3854	Gene expression profiling panel for use in the management of breast cancer treatment

Policy History

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

Effective Date	Action
12/01/2005	New Policy Adoption
03/12/2007	Policy Revision
04/03/2009	Policy Revision
01/11/2013	Policy revision with position change
01/23/2013	Coding update
09/27/2013	Policy revision without position change

Effective Date	Action
09/30/2014	Policy title change from Gene Expression Profiling for Managing Breast Cancer Treatment Policy revision with position change
01/01/2015	Coding update
01/01/2016	Coding update
07/01/2016	Coding update
06/01/2017	Policy revision with position change
10/01/2017	Policy revision without position change
01/01/2018	Policy revision without position change Coding update
07/01/2018	Policy revision without position change Coding update
01/01/2019	Policy revision without position change Coding update
10/01/2019	Policy revision without position change
02/01/2020	Annual review. Policy statement, guidelines and literature updated. Coding update
03/01/2020	Coding update
11/01/2020	Policy statement and guidelines updated.
01/01/2021	Annual review. Policy statement and literature updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

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

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

Prior Authorization Requirements (as applicable to your plan)

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

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

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

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients With Breast Cancer 2.04.36 **Policy Statement:** The use of a multi-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (i.e., Oncotype DX®), as well as EndoPredict®, the Breast Cancer Index℠, MammaPrint®, and Prosigna®, to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy, in women with primary, invasive breast cancer may be considered **medically necessary** when **all** of the following characteristics are met: I. Patient has unilateral tumor II. Patient is hormone receptor-positive (i.e., estrogen receptor [ER]-positive or progesterone receptor [PR]-positive) III. Patient is human epidermal growth factor receptor 2 (*HER2*)-negative IV. Documentation of **one or more** of the following: A. Tumor size 0.6 to 1 centimeter (cm) with moderate or poor differentiation or unfavorable features B. Tumor size larger than 1 cm V. Documentation of **one or more** of the following: A. Patient is node-negative (lymph nodes with micrometastases [less than or equal to 2 millimeters (mm) in size] are considered node-negative for this policy statement) B. Up to three positive nodes when the test is for MammaPrint or Oncotype DX AND the patient is in stage T1, T2 or operable T3 AND at high clinical risk VI. Patient will be treated with adjuvant endocrine therapy (e.g., tamoxifen, aromatase inhibitors) VII. The test result aids the patient in deciding on chemotherapy (i.e., when chemotherapy is a therapeutic option) VIII. Ordered within 6 months after diagnosis, because the value of the test for making decisions regarding delayed chemotherapy is unknown	**Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer 2.04.36** **Policy Statement:** The use of the multi-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (i.e., Oncotype DX®), as well as EndoPredict®, the Breast Cancer Index℠, MammaPrint®, and Prosigna®, to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy in women with primary, invasive breast cancer may be considered **medically necessary** when **all** of the following characteristics are met: I. Patient has unilateral tumor II. Patient is hormone receptor-positive (i.e., estrogen receptor-positive or progesterone receptor [PR]-positive) III. Patient is human epidermal growth factor receptor 2 (*HER2*)-negative IV. Documentation of **one or more** of the following: A. Tumor size 0.6 to 1 centimeter (cm) with moderate or poor differentiation or unfavorable features B. Tumor size larger than 1 cm V. Documentation of **one or more** of the following: A. Patient is node-negative (lymph nodes with micrometastases [less than or equal to 2 millimeters (mm) in size] are considered node-negative for this policy statement) B. Up to three positive nodes when the test is for MammaPrint or Oncotype DX AND the patient is in stage T1, T2 or operable T3 AND at high clinical risk VI. Patient will be treated with adjuvant endocrine therapy (e.g., tamoxifen, aromatase inhibitors) VII. The test result aids the patient in deciding on chemotherapy (i.e., when chemotherapy is a therapeutic option) VIII. Ordered within 6 months after diagnosis, because the value of the test for making decisions regarding delayed chemotherapy is unknown

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
The following conditions are considered **investigational:** I. All other indications for the 21-gene RT-PCR assay (i.e., Oncotype DX®), EndoPredict®, the Breast Cancer Index℠, MammaPrint®, and Prosigna®, including determination of recurrence risk in invasive breast cancer patients with positive lymph nodes (except Mammaprint when there are less than 4 positive nodes), patients with bilateral disease, or to consider the length of treatment with tamoxifen II. Use of a subset of genes from the 21-gene RT-PCR assay for predicting recurrence risk in patients with noninvasive ductal carcinoma in situ (i.e., Oncotype DX® Breast Ductal Carcinoma in Situ [DCIS] Score) to inform treatment planning after excisional surgery III. The use of BluePrint® (either in conjunction with MammaPrint or alone) IV. Use of gene expression assays in men with breast	The following conditions are considered **investigational:** I. All other indications for the 21-gene RT-PCR assay (ie, Oncotype DX®), EndoPredict®, the Breast Cancer Index℠, MammaPrint®, and Prosigna®, including determination of recurrence risk in invasive breast cancer patients with positive lymph nodes (except Mammaprint when there are less than 4 positive nodes), patients with bilateral disease, or to consider the length of treatment with tamoxifen II. Use of a subset of genes from the 21-gene RT-PCR assay for predicting recurrence risk in patients with noninvasive ductal carcinoma in situ (i.e., Oncotype DX® Breast Ductal Carcinoma in Situ [DCIS] Score) to inform treatment planning after excisional surgery III. The use of BluePrint® (either in conjunction with MammaPrint or alone) IV. The use of Insight TNBCtype to aid in making decisions regarding chemotherapy in women with triple-negative breast cancer V. Use of gene expression assays in men with breast cancer