Medical Policy

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

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Populations	Interventions	Comparators	Outcomes
Individuals: • With early-stage node-negative invasive breast cancer considering adjuvant chemotherapy	Interventions of interest are: • Gene expression profiling with Oncotype DX (21-gene signature)	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With early-stage node-negative invasive breast cancer considering adjuvant chemotherapy	Interventions of interest are: • Gene expression profiling with EndoPredict	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With early-stage node-negative invasive breast cancer considering adjuvant chemotherapy	Interventions of interest are: • Gene expression profiling with the Breast Cancer Index	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With early-stage node-negative invasive breast cancer considering adjuvant chemotherapy	Interventions of interest are: • Gene expression profiling with MammaPrint (70-gene signature)	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With early-stage node-negative invasive breast cancer considering adjuvant chemotherapy	Interventions of interest are: • Gene expression profiling with Prosigna	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With early-stage node-positive (1 to 3 nodes) invasive breast cancer considering adjuvant chemotherapy	Interventions of interest are: • Gene expression profiling with Oncotype DX (21-gene signature)	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With early-stage node-positive (1 to 3 nodes) invasive breast cancer considering adjuvant chemotherapy	Interventions of interest are: • Gene expression profiling with EndoPredict	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With early-stage node-positive (1 to 3 nodes) invasive breast cancer considering adjuvant chemotherapy	Interventions of interest are: • Gene expression profiling with MammaPrint (70-gene signature)	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals:	Interventions of interest are:	Comparators of interest are:	Relevant outcomes include:

Populations	Interventions	Comparators	Outcomes
• With early-stage node-positive (1 to 3 nodes) invasive breast cancer considering adjuvant chemotherapy	Gene expression profiling with Prosigna	• Clinical risk prediction algorithms	• Disease-specific survival • Change in disease status
Individuals: • With ductal carcinoma in situ considering radiotherapy	Interventions of interest are: • Gene expression profiling with the Oncotype DX Breast DCIS Score	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Change in disease status
Individuals: • With ductal carcinoma in situ considering radiotherapy	Interventions of interest are: • Gene expression profiling with the DCISionRT assay	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Change in disease status
Individuals: • With early-stage node-negative invasive breast cancer, recurrence-free at 5 years, considering extended endocrine therapy	Interventions of interest are: • Gene expression profiling with Oncotype DX (21-gene signature)	Comparators of interest are: Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With early-stage node-negative invasive breast cancer, recurrence-free at 5 years, considering extended endocrine therapy	Interventions of interest are: • Gene expression profiling with EndoPredict	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With early-stage node-negative invasive breast cancer, recurrence-free at 5 years, considering extended endocrine therapy	Interventions of interest are: • Gene expression profiling with the Breast Cancer Index	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With early-stage node-negative invasive breast cancer, recurrence-free at 5 years, considering extended endocrine therapy	Interventions of interest are: • Gene expression profiling with MammaPrint (70-gene signature)	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With early-stage node-negative invasive breast cancer, recurrence-free at 5 years, considering extended endocrine therapy	Interventions of interest are: • Gene expression profiling with Prosigna	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With early-stage node-negative invasive breast cancer, recurrence-free at 5	Interventions of interest are: • Gene expression profiling with the	Comparators of interest are:	Relevant outcomes include: • Disease-specific survival

Populations	Interventions	Comparators	Outcomes
years, considering extended endocrine therapy	Breast Cancer Index	• Clinical risk prediction algorithms	• Change in disease status
Individuals: • With triple-negative (estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2) breast cancer, considering neoadjuvant chemotherapy	Interventions of interest are: • Gene expression profiling with Insight TNBC type	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: •With breast cancer	Interventions of interest are: • Multiple (repeat) assays of genetic expression in tumor tissue performed on the same individual to determine prognosis	Comparators of interest are: • Gene expression profiling with a single assay	Relevant outcomes include: • Disease-specific survival • Change in disease status

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.

OBJECTIVE

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

BACKGROUND

Newly Diagnosed Breast Cancer

Per the Centers for Disease Control, breast cancer is a disease in which cells in the breast grow out of control, and can be found in the lobules, ducts, and connective tissue.[1,] The most common breast cancers are invasive ductal carcinoma and invasive lobular carcinoma. Less common types of breast cancer include Paget's disease, medullary, mucinous, and inflammatory. In ductal carcinoma in situ (DCIS), the cancer cells are only in the lining of the ducts and have not spread to other tissues; DCIS may lead to invasive breast cancer. Breast cancer affects individuals of all races and ethnicities and sexes. New cases are highest among White women (130.3 per 100,000) followed by Black women (125.4 per 100,000). Rates of death from breast cancer, however, are

highest among Black women (26.8 per 100,000) followed by White women (18.8 per 100,000). Most breast cancer diagnoses are female breast cancer diagnosed at a localized stage (confined to the primary site), with less diagnoses being regional (spread beyond the primary site or to regional lymph nodes) or distant (spread to other organs or remote lymph nodes). The Nottingham score is a histological scoring system reflecting the grade of breast cancers. It is a total of scores based on microscopic determination of tubule formation, nuclear pleomorphism, and mitotic activity with each given a score of 1 to 3. Thus, the lowest Nottingham score is 3 and the highest is 9, with higher values thought to predict more aggressiveness. Nottingham score of 3-5 is assigned Grade I, 6-7 assigned Grade II, and 8-9 assigned Grade III.

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.[2,] 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.8.2021) include various recommendations and considerations, based on menopausal status at diagnosis and after 5 years of therapy, and on prior therapy history (see Supplemental Information section). The guidelines also note that the optimal duration of AIs is uncertain.[3,] The American Society for Clinical Oncology's updated guidelines (2018) vary based on recurrence risk and nodal status (see Supplemental Information section).[4,5,]

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% to 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.[6,] 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).[2,] 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 (eg, 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[7,]; 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).[2,]
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.[8,]

Early randomized trials of extended tamoxifen treatment: (Tormey et al [1996]; total N=194 patients),[9,] the National Surgical Adjuvant Breast and Bowel Project (Fisher et al [2001]; total N=1172 patients),[10,] and the Scottish Cancer Trials Breast Group (Stewart et al [2001]; total N=342 patients)[11,] had mixed findings. However, more recent available trial evidence suggests that 10 years of tamoxifen in pre- or postmenopausal women can be linked with improved survival (see Table 2).

These randomized controlled trials have shown that extended endocrine therapy decreases the risk of recurrence. The Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial, which compared 5 and 10 years of tamoxifen,[12,] and the subsequent Long-term Effects of Continuing Adjuvant Tamoxifen to 10 Years versus Stopping at 5 Years (aTTom) trial (reported in abstract form)[13,] 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 versus placebo following several years of tamoxifen,[14,15,16,17,] and 2 trials compared the use of extended AIs for different durations (3 years vs. 6 years[18,] and 2.5 years versus 5 years[19,20,]) (see Table 2). No differences in OS were detected between the AI groups and 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 (eg, 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.[21,22,] Women treated with AIs have also experienced higher fracture rates compared with women treated with tamoxifen.[23,]

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)[12,]	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)	.01	• 0.87 (0.78 to 0.97) • 722 (639/3428 vs. 722/3418)	0.01
aTTom (2013)[13,]	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)	.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

Study	Population	Comparators	Breast Cancer-Specific Mortality		Overall Mortality	
			Event RR (95% CI)	***p***	***Event RR (95% CI)***	***p***
Extended aromatase inhibitor						
ABCSG (2007)[14,]	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
IDEAL (2018)[19,]	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 and: 82.0% • 5 and: 83.3%	.50	Median 6.6 Years • 2.5 and: 89.4% • 5 and: 88.6%	NS
DATA (2017) [18,]	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 and: 79.4% • 6 and: 83.1%	.06	5 Years • 3 and: 90.4% • 6 and: 90.8%	0.6
NSABP (2008)[17,]	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	48 Months • ITT: 91% exemestane vs. 89% placebo	.07		

Study	Population	Comparators	Breast Cancer-Specific Mortality		Overall Mortality	
			Event RR (95% CI)	***p***	***Event RR (95% CI)***	***p***
		Placebo: 779 randomized, 334 crossed over to exemestane after unblinding				
NCIC CTG MA.17 trial (2003, 2005)[15,16,]	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)	<.001	4 8 Months • 95.4% letrozole vs. 95% placebo Event HR • 0.82 (0.57 to 1.19)	0.3
SALSA NCT00295620 Gnant et al (2021)[20,]	3,470 post-menopausal women with hormone-receptor-positive early stage breast cancer who had received 5 years of adjuvant endocrine therapy	Aromatase inhibitor for an additional 2 years (total 7 years) vs. an additional 5 years (total 10 years)	Disease recurrence or death 10 years: 73.6% vs. 73.9% HR 0.99 (95% CI 0.85 to 1.15)	.90	10 years: 87.5% vs. 87.3% HR 1.02 (0.83 to 1.25)	NS

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; SALSA: Secondary Adjuvant Long-Term Study with Arimidex [anastrozole]; 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.[24,] 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 (eg, withholding of chemotherapy), and the study must have sufficient precision (narrow confidence intervals). Results of the same test across studies should show the consistency of results and more than 1 study demonstrating the desired result should be available. Simon 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.[24,] 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."[24,]

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), Insight TNBCtype (Insight Genetics), and DCISionRT (PreludeDX) are not FDA cleared or approved.

POLICY

A. The use of the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (i.e., Oncotype DX), EndoPredict, the Breast Cancer Index, MammaPrint, or Prosigna to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy may be considered **medically necessary** in women with primary, invasive, node-negative breast cancer meeting **ALL** of the following characteristics:
   1. unilateral tumor (see Policy Guidelines); **AND**
   2. hormone receptor-positive (i.e., estrogen-receptor positive or progesterone receptor positive); **AND**
   3. human epidermal growth factor receptor 2 negative; **AND**
   4. tumor size 0.6 to 1 cm with moderate or poor differentiation or unfavorable features OR tumor size larger than 1 cm; **AND**
   5. node negative (lymph nodes with micrometastases [less than or equal to 2 mm in size] are considered node negative for this policy statement); **AND**
   6. who will be treated with adjuvant endocrine therapy, (e.g., tamoxifen aromatase inhibitors); **AND**
   7. when the test result aids the individual in deciding on chemotherapy (i.e., when chemotherapy is a therapeutic option); **AND**
   8. when ordered within 6 months following diagnosis, because the value of the test for making decisions regarding delayed chemotherapy is unknown.

B. The use of the MammaPrint assay to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy may be considered **medically necessary** in women with primary, invasive, node positive breast cancer meeting **ALL** of the following characteristics:
   1. unilateral tumor; **AND**
   2. hormone receptor-positive (i.e., estrogen receptor-positive or progesterone receptor-positive); **AND**
   3. human epidermal growth factor receptor 2-negative; **AND**
   4. stage T1 or T2 or operable T3 at high clinical risk (see Policy Guidelines); **AND**
   5. one to three positive nodes (N1); **AND**
   6. no distant metastases; **AND**
   7. who will be treated with adjuvant endocrine therapy (e.g., tamoxifen, aromatase inhibitors); **AND**
   8. eligible for a chemotherapy regimen containing a taxane, an anthracycline, or both; **AND**
   9. when the test result aids the individual in deciding on chemotherapy (i.e., when chemotherapy is a therapeutic option); **AND**
   10. when ordered within 6 months after diagnosis, because the value of the test for making decisions regarding delayed chemotherapy is unknown.

C. The use of Oncotype Dx to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy may be considered **medically necessary** in women with primary, invasive, node positive breast cancer meeting **ALL** of the following characteristics:
   1. postmenopausal (defined as previous bilateral oophorectomy or more than 12 months since the last menstrual period and no previous hysterectomy);
   2. unilateral tumor; **AND**
   3. hormone receptor-positive (ie, estrogen receptor-positive or progesterone receptor-positive); **AND**
   4. human epidermal growth factor receptor 2-negative; **AND**
   5. stage T1 or T2 or operable T3 at high clinical risk (see Policy Guidelines); **AND**
   6. 1 to 3 positive nodes (N1); **AND**
   7. no distant metastases; **AND**
   8. who will be treated with adjuvant endocrine therapy (eg, tamoxifen, aromatase inhibitors); **AND**
   9. eligible for a chemotherapy regimen containing a taxane, an anthracycline, or both; **AND**
   10. when the test result aids the patient in deciding on chemotherapy (ie, when chemotherapy is a therapeutic option); **AND**
   11. when ordered within 6 months after diagnosis, because the value of the test for making decisions regarding delayed chemotherapy is unknown.

D. The use of Oncotype Dx to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy in premenopausal women (defined as less than 6 months since the last menstrual period) with primary, invasive, node positive breast cancer is considered **experimental / investigational** (see Policy Guidelines).

E. The use of EndoPredict, the Breast Cancer Index, and Prosigna to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy in individuals with primary, invasive, node positive breast cancer is considered **experimental / investigational**.

F. The 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-individual discussion regarding risk preferences when the test result will aid in making decisions regarding chemotherapy.

G. For individuals who otherwise meet the above characteristics but who have multiple ipsilateral primary tumors, a specimen from the tumor with the most aggressive histological characteristics should be submitted for testing. It is not necessary to test each tumor; treatment is based on the most aggressive lesion (see Policy Guidelines).

H. All other indications for the 21-gene RT-PCR assay (i.e., Oncotype DX), EndoPredict, the Breast Cancer Index, MammaPrint, and Prosigna, including to consider the length of treatment with endocrine therapy, repeat testing with same test, or combination testing with various tests, are considered **experimental / investigational**.

I. Use of a subset of genes from the 21-gene RT-PCR assay for predicting recurrence risk in individuals with noninvasive ductal carcinoma in situ (i.e., Oncotype DX Breast DCIS Score) to inform treatment planning after excisional surgery is considered **experimental / investigational**.

J. Use of the DCISion RT assay for predicting recurrence risk in individuals with noninvasive ductal carcinoma in situ to inform treatment planning after excisional surgery is considered **experimental / investigational**.

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

L. The use of Insight TNBCtype to aid in making decisions regarding chemotherapy in women with triple-negative breast cancer is considered **experimental / investigational**.

M. Use of gene expression assays in men with breast cancer is considered **experimental / investigational**.

POLICY GUIDELINES

A. Unilateral Bilateral Premenopausal

Most breast cancer is unilateral, occurring in one breast. Bilateral breast cancer, breast cancer in both breasts, can be synchronous or metachronous. Synchronous is generally defined as occurring within 6 months, but other intervals are used (3 months or even 12 months), and overall, inconsistency in the use of the term "bilateral breast cancer" occurs. It is difficult to clearly know if a second breast cancer appearing within months of the first is metastatic spread or a new primary. There are no professional guidelines on use of gene expression assays in bilateral breast cancers, although small studies show Oncotype Dx score discordancy in synchronous bilateral ER-positive HER2-negative breast cancer with associated chemotherapy recommendation changes of 50% to 57%. No health outcomes were reported from the change in chemotherapy recommendations. As such, the position relates only to unilateral breast cancer although at the local level consideration could be given to genetic expression assay in a second cancer in the contralateral breast.

B. Premenopausal

The position on premenopausal women with node positive breast cancer differs from the NCCN guidelines (https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf). The NCCN guidelines have a 2A recommendation for OncotypeDx testing of premenopausal women with 1-3 positive lymph nodes based on the RxPONDER trial (Kalinsky et. al., 2021; PMID 34914339). Based on this test, the NCCN guidelines have a recommendation to "consider chemotherapy followed by endocrine therapy or alternatively, ovarian function suppression combined with either tamoxifen or an Aromatase inhibitor." Note that RxPONDER was not designed to test whether chemotherapy can be replaced by ovarian suppression, and that among premenopausal women, invasive disease–free survival at 5 years was 89.0% with endocrine-only therapy and 93.9% with chemoendocrine therapy (hazard ratio, 0.60; 95% CI, 0.43 to 0.83; P = 0.002), with a similar increase in distant relapse–free survival (hazard ratio, 0.58; 95% CI, 0.39 to 0.87; P = 0.009) indicating benefit of chemoendocrine therapy. While the evidence then is insufficient to support Oncotype DX testing as perhaps all premenopausal women benefit from chemoendocrine therapy

regardless of Oncotype DX recurrence score, with the NCCN 2A recommendation for using Oncotype Dx testing for premenopausal women a local decision might need to be made.

C. **Clinical Risk**

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 individuals were classified as high clinical risk if they met any of the following additional criteria:

1. Grade: well differentiated; tumor size: 2.1 to 5 cm
2. Grade: moderately differentiated; tumor size: any size
3. Grade: poorly differentiated or undifferentiated; tumor size: any size

D. **Multiple Ipsilateral Tumors**

Gene expression assay testing on multiple ipsilateral primary tumors could start with assessing the most histologically aggressive, as concordance of Oncotype Dx score with Nottingham score is strong. However, a low Oncotype Dx score indicating no need for adjuvant chemotherapy from the most aggressive appearing tumor might not negate the need for Oncotype Dx testing of other primary tumors. The literature base for this strategy is slim; but, for ipsilateral multiple tumors, Toole, et al. show that 22% (4 out of 18) had Oncotype Dx score differences that led to changes in management. Additionally though, Toole, et al. found that in a small number of cases the histology and grade were the same on ipsilateral lesions yet had significantly different Oncotype Dx scores altering chemotherapy recommendations. Larger, prospective studies are needed including clinical outcomes from management changes. Consideration at the local level could be given to histologically distinct tumors meeting the other criteria for gene expression assay testing, or serial testing. There is no literature assessing the use of one gene expression assay on one tumor and a different gene expression assay on another ipsilateral tumor.

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.

RATIONALE

This evidence review has been updated regularly with searches using the PubMed database. The most recent literature update was performed through September 13, 2022.

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^{SM} 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

Test	Manufacturer	Description
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
DCISionRT	PreludeDx	Combines 7 monoclonal protein markers (COX-2, FOXA1, HER2, Ki-67, p16/INK4A, PR, and SIAH2) assessed in tumor tissue with 4 clinicopathologic factors (age at diagnosis, tumor size, palpability, and surgical margin status) to produce a score that stratifies individuals with DCIS into 3 risk groups: low risk, elevated risk with good response, and elevated risk with poor response. The purpose of the test is to predict radiation benefit in individuals with DCIS following breast conserving surgery.

DCIS: ductal carcinoma in situ; 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 (eg, Adjuvant! Online) estimates recurrence risk by considering criteria such as tumor size, type, grade, and histologic characteristics; hormone receptor status; and lymph node status. No single classifier is considered a criterion standard. Several common criteria have qualitative or subjective components that add variability to risk estimates.

A risk classifier tool to guide the use of extended therapy has been developed and validated in 2018 (Clinical Treatment Score post-5 years [CTS5]) but was not available at the time the studies providing evidence in this review were conducted.

Outcomes

Outcomes of interest for all assays are disease-specific survival and change in disease status.

- If patients with early-stage invasive breast cancer are classified as low-risk for distant recurrence, they may be able to forgo adjuvant chemotherapy safely.
- If patients with DCIS are classified as low-risk for distant recurrence, they may be able to safely forgo radiotherapy.
- If patients with invasive breast cancer who are recurrence-free for 5 years are classified as low-risk for distant recurrence, they may be able to safely forgo extended endocrine therapy.
- 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.[25,] 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.[26,] 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.[27,28,] 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.[29,] 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.[30,] 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.[31,] 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.[32,] 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).[33,]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).[33,]

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.[24,]. 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.[24,]

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.[24,]

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.[24,]

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.[24,]

REVIEW OF EVIDENCE

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

ONCOTYPE DX (21-GENE ASSAY)

Low-Risk Threshold (Recurrence Scores ≤10)
BCBSA identified 4 studies with 10 year outcomes meeting selection criteria for the low-risk category.[34,35,36,37,] 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.[36,] The study by Tang et al (2011)[37,] represents the same results as Paik et al (2004),[35,] 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),[32,] 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).[38,] 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 10,253 subjects, 1629 patients had a RS of 0 to 10 and did not receive adjuvant chemotherapy (it should be noted that the cutoff score of 10 is lower than that for other studies evaluating Oncotype DX and thus evaluates a group at lower predicted risk of distant recurrence than other Oncotype DX studies, which typically used a cutoff of 18). Consequently, only 15.9% of the study population was judged low-risk, which is much lower than 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.

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 (Table 5).

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)[35], (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)[36], (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)[37], (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)[34], (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) [39], (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.

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.[40] 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 6. Survival and Distant Recurrence Estimates by Oncotype DX RS in TAILORx[40]

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)

RS	Therapy	DFS Rate (SD)		Free From DR Rate (SD)		OS Rate (SD)	
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.

Subsection 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. n 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.[40,]

EndoPredict
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.[41,] 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 versus tamoxifen in postmenopausal women with localized breast cancer.[34,39,] 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.[42,] 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=.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.

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)[41,,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)[41,,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)[34,](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)[39,] (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.

Subsection 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

BCBSA identified 4 sets of findings using samples from 2 RCTs and a registry for the BCI that met selection criteria (see Table 8).[43,44,] Some *HER2*-positive patients were included in both studies but the number was not provided. Sgroi et al (2013)[43,] and Sestak et al (2018)[39,] 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.[44,] 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%.

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)[44,] (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)[44,] (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*
Sgroi et al (2013)[43,] (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)[39,] (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.

Subsection 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. 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.

MammaPrint (70-Gene Signature)

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 9).[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%). Piccart et al reported updated results from MINDACT in 2021.[46,] In the updated analysis, with median follow-up of 8.7 years (IQR 7.8 to 9.7), 5-year distant metastasis-free survival rate for individuals with high clinical risk and low genomic risk receiving no chemotherapy (primary test population, n=644) was 95.1% (95% CI 93.1% to 96.6%), supporting the previous analysis.

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 9. 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.

Subsection 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]), The Simon et al (2009) category A study of MammaPrint 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
Three studies using samples from 2 RCTs that met selection criteria were identified (studies are classed as Simon et al [2009] category B).[47,48,39,] However, the distant recurrence rates from the study by Dowsett et al (2013) were not directly reported in the published article. As a result, rates cited in Table 10 are based on visual estimates of the graphic results; CIs are not available.).[47,] 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.

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 10. 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) [48,] (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)

Study (Trial)	N	Risk Score Group (% Patients in Risk Group)			10-Year Distant Recurrence (95% Confidence Interval), %		
Dowsett et al (2013)[47,] (ATAC trial)	739	59	33	8	4.8 (NR)	13.8 (NR)	30.2 (NR)
Sestak et al (2018) [39,] (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.

Subsection 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.

Section Summary: Early-Stage Node-Negative Invasive Breast Cancer Considering Adjuvant Chemotherapy

Table 11 summarizes the level of evidence for each test in early-stage node-negative breast cancer. Because the evidence includes at least 2 Simon Category Level B studies or 1 Category Level A study, the evidence is sufficient for each.

Table 11. Summary of the Evidence for Early-Stage Node-Negative Invasive Breast Cancer Considering Adjuvant Chemotherapy

Test	Highest Level of Evidence (citations)	Sufficiency of the Evidence
Oncotype DX	2 Simon Category A	Sufficient
EndoPredict	4 Simon Category B	Sufficient
Breast Cancer Index	2 Simon Category B	Sufficient
MammaPrint	1 Simon Category A	Sufficient
Prosigna	3 Simon Category B	Sufficient

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

Table 12 summarizes the clinical validity studies that met selection criteria , 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. 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 13 displays 10-year event rates by risk categories in these studies.

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

Study	N	ER +	*HER 2+*	Tumor Size			Nodes		Adjuvant Chemo	Trial/Study
				≤2 cm	*2-5 cm*	*>5 cm*	*1-3*	*≥4*		
Oncotype DX										
Albain (2010)[49,,a]	148	145 (98)	13 (9)	46 (31)	94 (64)	8 (5)	94 (64)	54 (36)	0 (0)	SWOG-8814
Albain (2010)[49,,b]	219	210 (96)	30 (14)	74 (34)	136 (62)	9 (4)	133 (61)	86 (39)	219 (100)	
Dowsett (2010)[50,]	306	306 (100)	NR for node-positive patients				243 (79)	63 (21)	0 (0)	TransATAC
Nitz (2017)[51,] Nitz (2019)[52,]	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)[39,]	183	183 (100)	0 (0)	NR			183 (100)	0	0 (0)	TransATAC
EndoPredict										
Filipits (2011)[41,]Filipts (2019)	537	537 (100)	0 (0)	NR for node-positive patients			454 (85)	83 (15)	0 (0)	ABCSG-6, ABCSG-8
Buus (2016)[34,]	248	248 (100)	0 (0)	NR for node-positive patients			198 (80)	50 (20)	0 (0)	TransATAC
Sestak (2018)[39,]	183	183 (100)	0 (0)	NR			183 (100)	0	0 (0)	TransATAC
Prosigna										
Gnant (2015)[53,]	543		28 (5)	314 (58)			229 (42)	0 (0)	543 (100)	ABCSG-8
Sestak (2018)[39,]	183	183 (100)	0 (0)	NR			183 (100)	0	0 (0)	TransATAC

Study	N	ER +	*HER2*+	Tumor Size	Nodes		Adjuvant Chemo	Trial/Study
Breast Cancer Index								
Sestak (2018)[39,]	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. 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)[49,a]	148	55	60 (NR)	46	49 (NR)	47	43 (NR)
		n	*OS % (95% CI)*	*n*	*OS % (95% CI)*	*n*	*OS % (95% CI)*
Albain (2010)[49,b]	148	55	77 (NR)	46	68 (NR)	47	51 (NR)
Dowsett (2010)[50,]	296	150	74 (NR)	94	69 (NR)	52	54 (NR)
		n	*DR % (95% CI)*	*n*	*DR % (95% CI)*	*n*	*DR % (95% CI)*
Dowsett (2010)[50,a]	296	150	17 (12 to 24)	94	28 (20 to 49)	52	49 (35 to 54)
Sestak (2018)[39,]	183	105	19 (13 to 29)	58	29 (19 to 43)	20	38 (20 to 64)
EndoPredict							
Filipits (2011)[41,] (EP)	537	240	15 (NR)	NA	NA	297	27 (NR)
Filipits (2019) [54,] (EPclin)	536	159	4.4 (0.9 to 7.8)	NA	NA	377	24.2 (19.1 to 29.0)
Buus (2016)[34,a] (EP)	248	94	21 (14 to 32)	NA	NA	154	36 (29 to 45)
Buus (2016)[34,a] (EPclin)	248	47	5 (1 to 19)	NA	NA	201	37 (30 to 45)
Sestak (2018)[39,] (EPclin)	183	43	5 (1 to 21)	NA	NA	140	30 (23 to 39)
Prosigna							
Gnant (2015)[53,b] (total)	331	132	7 (2 to 13)	106	15 (9 to 25)	93	25 (17 to 36)
Gnant (2015)[53,b] (≥2 nodes)	212			83[c]	12 (7 to 23)	129	34 (25 to 44)
Sestak (2018)[39,]	183	15	0	58	21 (12 to 34)	110	31 (22 to 41)
Breast Cancer Index							
Sestak (2018)[39,]	183	95	15 (9 to 25)	60	32 (21 to 47)	28	41 (24 to 64)

CI: confidence interval; DFS: disease-free survival; DR: distant recurrence; EP: expression profile score; EPclin: EndoPredict score; NA: not applicable; NR: not reported; OS: overall survival.
[a] Death from any cause considered a censoring event.
[b] Death from breast cancer included as a distant recurrence.
[c] Combined low- and intermediate-risk categories.

Oncotype DX (21-Gene Assay)
Kalinsky et al (2021) reported results from the RxPONDER RCT (NCT01272037).[55,]Participants with hormone-receptor–positive, HER2-negative breast cancer, 1 to 3 positive axillary lymph nodes, and a RS of 25 or lower were randomized to endocrine therapy only or to chemotherapy plus endocrine (chemoendocrine) therapy. The primary objective was to determine the effect of chemotherapy on invasive disease–free survival and whether the effect was influenced by the RS Secondary end points included distant relapse–free survival.

Among postmenopausal women, Estimates of invasive disease–free survival at 5 years were 91.3% in the chemoendocrine group and 91.9% in the endocrine-only group (hazard ratio for invasive disease recurrence, new primary cancer [breast cancer or another type], or death, 1.02; 95% CI, 0.82 to 1.26; P = 0.89). In premenopausal women, the rate of invasive disease–free survival at 5 years among those in the chemoendocrine group was 93.9%, as compared with 89.0% among those in the endocrine-only group (absolute difference, 4.9 percentage points), with a significant chemotherapy benefit (hazard ratio for invasive disease recurrence, new primary cancer [breast cancer or another type], or death, 0.60; 95% CI, 0.43 to 0.83; P = 0.002).

The study authors concluded that "postmenopausal women with 1 to 3 positive axillary lymph nodes and a recurrence score of 0 to 25 were able to safely forgo adjuvant chemotherapy without compromising invasive disease–free survival and distant relapse–free survival. In contrast, premenopausal women with 1 to 3 positive lymph nodes had a significant benefit from chemotherapy, even with a very low recurrence score.

Subsection Summary: Oncotype DX (21-Gene Assay)
The RxPONDER RCT provided Simon Category A evidence that postmenopausal women with an Oncotype DX RS score of 0 to 25 could safely forego adjuvant chemotherapy without compromising invasive disease–free survival or distant relapse–free survival. Participants (N = xxx) with hormone-receptor–positive, HER2-negative breast cancer, 1 to 3 positive axillary lymph nodes, and a RS of 25 or lower were randomized to endocrine therapy only or to chemotherapy plus endocrine (chemoendocrine) therapy. Among postmenopausal women, estimates of invasive disease–free survival at 5 years were 91.3% in the chemoendocrine group and 91.9% in the endocrine-only group (hazard ratio for invasive disease recurrence, new primary cancer [breast cancer or another type], or death, 1.02; 95% CI, 0.82 to 1.26; P =.89). In premenopausal women, the rate of invasive disease–free survival at 5 years among those in the chemoendocrine group was 93.9%, as compared with 89.0% among those in the endocrine-only group (absolute difference, 4.9 percentage points), with a significant chemotherapy benefit (hazard ratio for invasive disease recurrence, new primary cancer [breast cancer or another type], or death, 0.60; 95% CI, 0.43 to 0.83; P =.002).

EndoPredict
The prognostic value of EndoPredict among node-positive patients has been evaluated in 1 prospective study[56,] and 2 prospective-retrospective studies.[34,41,] 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 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).[34,] 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).[41,] 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.[54,] 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.

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%.

Subsection 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%. One study had a precise estimate while the other study had wide CIs, and the upper bound for the 95% CI was 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)
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=.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.

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
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.[53,] 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.

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%.

Subsection Summary: Prosigna
One Simon et al (2009) category B study (Gnant et al [2015]) meeting inclusion criteria was identified. The 10 year distant recurrence rate in patients with a single positive node and low-risk ROR scores is about 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.

Section Summary: Early-Stage Node-Positive Invasive Breast Cancer Considering Adjuvant Chemotherapy

Table 14 summarizes the level of evidence for each test in node-positive breast cancer. Evidence for Oncotype Dx and the BCI includes 1 Simon Category A study and thus the evidence is sufficient. Additional evidence is required for EndoPredict, the BCI, and Prosigna.

Table 14. Summary of the Evidence for Early-Stage Node-Positive Invasive Breast Cancer Considering Adjuvant Chemotherapy

Test	Highest Level of Evidence (citations)	Sufficiency of the Evidence[1]
Oncotype DX	1 Simon Category A (Kalinsky 2021)[55,]	Sufficient
EndoPredict	2 Simon Category B (Buus 2016,[34,] Filipits 2011) 1 study imprecise estimate (CI exceeded 10% precision threshold)	Insufficient
Breast Cancer Index	No studies meeting inclusion criteria	Insufficient
MammaPrint	1 Simon Category A (Cardoso 2016)[45,]	Sufficient
Prosigna	1 Simon Category B (Gnant 2015)[53,]	Insufficient

[1]An evidence sufficient determination requires at least 1 Simon Category A study or 2 Simon Category B studies with precise estimates of effect (CI 10% or lower).

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.

Oncotype DX Breast DCIS Score

The Oncotype DX Breast DCIS Score uses information from 12 of the 21 genes assayed in the standard Oncotype DX test for early breast cancer to predict 10-year risk of local recurrence (DCIS or invasive carcinoma). The stated purpose is to help guide treatment decision-making in women with DCIS treated by local excision, with or without adjuvant tamoxifen therapy.

In a retrospective analysis of data and samples from patients in the prospective Eastern Cooperative Oncology Group E5194 study, Solin et al (2013) compared 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 (Table 15).[57,] 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=.02) whether or not

patients were treated with tamoxifen. Ten-year recurrence risks by the DCIS category are listed in Table 16. Whether women are better categorized as to their local recurrence risk by Oncotype DX Breast DCIS Score compared with standard clinical indicators of risk was not addressed.

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.

Table 15. Retrospective Study Evaluating the Oncotype DX DCIS Score-Characteristics

Study	Country	Study Population	Design	N	Median FU, y
Solin et al (2013)[57,]	Canada	Patients with DCIS who had breast-conserving surgery without RT, from ECOG E5194 study	Retrospective	327	8.8

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

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

Study	N	Patients by Risk Score Group, %			Events	10-Year Recurrence Rates (95% Confidence Interval), %		
		Low	*Int*	*High*		*Low*	*Int*	*High*
Solin et al (2013)[57,]								
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 are shown in Tables 17 and 18.

Table 17. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator [c]	Outcomes[d]	Duration of Follow-Up[e]
Solin et al (2013)[Solin LJ, Gray R, Baehner FL, et al. A multigene e.... 105(10): 701-10. PMID 23641039]			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 18. 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)[Solin LJ, Gray R, Baehner FL, et al. A multigene e.... 105(10): 701-10. PMID 23641039]	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.

Subsection Summary: Oncotype DX Breast DCIS Score

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. Based on the Oncotype DX Breast DCIS Score of low-risk for recurrence (10.6% overall local recurrence; 95% CI 6.9 to 16.2), it is unclear whether estimated recurrence risks for this group are low enough to consider changing management. Additionally 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).

DCISionRT

The DCISionRT test combines 7 monoclonal protein markers (COX-2, FOXA1, HER2, Ki-67, p16/INK4A, PR, and SIAH2) assessed in tumor tissue with 4 clinicopathologic factors (age at diagnosis, tumor size, palpability, and surgical margin status) to produce a score that stratifies individuals with DCIS into 3 risk groups: low risk, elevated risk with good response, and elevated risk with poor response. The purpose of the test is to predict radiation benefit in individuals with DCIS following breast conserving surgery.

Warnberg et al analyzed the association of DCIS RT score with risk of recurrence in 504 individuals with DCIS enrolled in the SweDCIS randomized trial (Table 19).[58,] This study is Simon Category B. Using a cutoff of DS >3, 52% of participants were categorized as elevated risk and 48% as low risk. In the low risk group, there was no significant difference in risk of recurrence observed with radiotherapy. In contrast, radiotherapy was associated with reduced risk of total and invasive ipsilateral recurrence in the elevated risk group (see Table 20).

Three retrospective studies[59,60,61,]and one decision impact study without clinical outcomes[62,] did not meet inclusion criteria for this review.

Table 19. Retrospective Study Evaluating the DCISion RT Score- Characteristics

Study	Country	Study Population	Design	N
Warnberg et al (2021)[58,]	Sweden	Women diagnosed with DCIS from 1987 to 2000 who were randomly assigned to whole breast RT or no RT after BCS.	Prospective-retrospective	504

BCS: breast-conserving surgery; DCIS: ductal carcinoma in situ: radiotherapy.

Table 20. Ten-Year Local Recurrence by DCISionRT Score Groups

Study	10-Year Recurrence Rates (95% Confidence Interval), %	
Warnberg et al (2021)[58,]	Elevated Risk N = 264 (52%)	Low Risk N = 240 (48%)
Treated with BCS without RT		
Invasive BCE	7.7% (3.9% to 14.9%)	12.4% (7.2 to 20.8)
Total BCE	12.9% (6.9 to 23.5)	23.8 (14.8 to 36.8)

Study	10-Year Recurrence Rates (95% Confidence Interval), %	
Absolute risk difference		
Treated with BCS with RT		
Invasive BCE	3.1% (1.2% to 8.1%)	6.5% (3.2% to 13.2%)
Total BCE	8.3% (4.5% to 15.3%)	7.2% (3.5% to 14.6%)
Absolute risk difference: treated with RT vs no RT		
Invasive BCE	9.3% (2.0% to 16.5%)	1.2% (-5.7% to 8.2%)
Total BCE	15.5% (5.9% to 25.0%)	5.7% (-0.8% to 12.2%)

BC: breast cancer; DCIS: ductal carcinoma in situ

Subsection Summary: DCISion RT Score
One Simon et al (2009) category B study provided evidence for clinical validity which showed no benefit of radiation therapy among a group of participants classified as low risk using the DCIS RT score at a threshold of <3 (absolute risk difference for invasive recurrence 1.2% (-5.7% to 8.2%). However, it is unclear whether the estimated 10-year recurrence risk for this group (12.4%; 95% CI 7.2% to 20.8% for invasive recurrence) is low enough to consider changing management or is estimated with sufficient precision. 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 individuals with DCIS.

Section Summary: Ductal Carcinoma In Situ Considering Radiotherapy
Table 21 summarizes the level of evidence for each test in DCIS. Additional evidence from Simon Category A or B studies is required.

Table 21. Summary of the Evidence for Ductal Carcinoma In Situ Considering Radiotherapy

Test	Highest Level of Evidence (citations)	Sufficiency of the Evidence[1]
Oncotype DX Breast DCIS	1 Simon Category B (Solin et al, 2013)[57,]	Insufficient
DCISion RT	1 Simon Category B (Warnberg et al, 2021)[58,]	Insufficient

[1]An evidence sufficient determination requires at least 1 Simon Category A study or 2 Simon Category B studies with precise estimates of effect (CI 10% or lower).

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.[63,] 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).[64,] 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 22 summarizes the characteristics of studies that met selection criteria that examined the prognostic value of a gene expression profiling test for late distant recurrences after 10 years of endocrine therapy.[43,44,65,66,67,68,69,39,] 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)[44,] examining prognosis and an additional nested case-control study (Sgroi et al [2013])[70,] 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)[44,] included only postmenopausal women. Samples from several studies were used multiple times in analyses for the different molecular assays. Table 23 summarizes distant recurrence rates. Some studies provided results other than distant recurrence rates; those results appear in Tables 24, 25 and 26.

Table 22. 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)[68,]	940			683 (73)	257 (27)		0 (0)	TransATAC
Sestak (2018)[39,]	689			535 (78)	154 (22)		0 (0)	TransATAC
EndoPredict								
Dubsky (2013)[65,,a] Filipits (2019) [54,]	1702	1136 (67)	563 (33)	1165 (68)	454 (27)	83 (5)	0 (0)	ABCSG-6, ABCSG-8
Sestak (2018)[39,]	689			535 (78)	154 (22)		0 (0)	TransATAC
Breast Cancer Index								
Zhang (2013)[44,]	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)[43,]	597	442 (74)	155 (26)	597 (100)	0 (0)	0 (0)	0 (0)	TransATAC
Sgroi (2013)[70,]	249	110 (44)	139 (56)	94 (38)	146 (59)		148 (59)	Nested case-control in MA.17
Sestak (2018)[39,]	689			535 (78)	154 (22)		0 (0)	TransATAC
Bartlett et al (2019)[71,]	583	T1: 166 (46%) T2: 244 (42%) T3: 25 (4%) Unknown 48 (8%)		0(0%)	583 (100%)		0 (0%)	Trans-aTTom
Noordhoek et al (2021)[72,]	908	T1: 45% T2: 48%		26%	73%		0 (0%)	IDEAL
MammaPrint								
Esserman (2017)[69,]	652	499 (77)	145 (22)	652 (100)	0 (0)	0 (0)	0 (0)	Stockholm Trial TAM-treated
Prosigna								
Filipits (2014)[66,]	1246	NR (see below)		919 (74)	327 (26)		0 (0)	ABCSG-8

Study		Tumor Size, n (%)		Nodes, n (%)			Adjuvant Chemo, n (%)	Trial
Sestak (2013)[68,]	940			683 (73)	257 (27)		0 (0)	TransATAC
Sestak (2015),[67,] all patients	862	587 (68)	275 (32)	647 (75)	180 (21)	35 (4)	0 (0)	TransATAC
Sestak (2015),[67,] node-negative	1275	938 (74)	337 (26)	933 (73)	307 (24)	35 (3)	0 (0)	ABCSG-8
Sestak (2018)[39,]	689			535 (78)	154 (22)		0 (0)	TransATAC
CTS5								
Dowsett (2018)[64,]	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 theArimidex, Tamoxifen, Alone or in Combination.
[a] Sample size and characteristics represent patients at enrollment for Dubsky et al (2013).

Table 23. 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)[68,]	940	5-10	NR	7.6 (NR)	NR	NR	NR	17.6 (NR)
Sestak (2018)[39,]	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)[65,a] (EP)	998	5-10	503	3.7 (0.9 to 6.5)		NA	495	9.0 (NR)
Dubsky (2013)[65,a] (EPclin)	998	5-10	642	1.8 (0.1 to 3.5)		NA	356	13.0 (NR)
Filipits (2019)[54,] (EPclin); node-negative only Note: Longer follow-up of cohort from Dubsky (2013)	976	5-10	764	2.1 (0.9 to 3.3)		NA	212	5.9 (2.2 to 9.5)
		5-15	764	3.1 (1.5 to 4.8)		NA	212	15.1 (4.0 to 24.9)
Sestak (2018)[39,] (EPclin)	535	5-10	393	4.3 (2.6 to 7.1)		NA	142	14.6 (9.6 to 22.0)

Study			Low-Risk		Intermediate-Risk		High-Risk	
Breast Cancer Index								
Zhang (2013)[44,] (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)[44,] (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)[43,]	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)[39,]	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)[66,]	1246	5-15	460	2.4 (1.1 to 5.3)	416	9.1 (5.8 to 14.1)	370	17.6 (12.9 to 25.2)
Sestak (2013)[68,]	940	5-10	NR	4.1 (NR)	NR	NR	NR	NR
Sestak (2015),[67,] 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),[67,] 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)[39,]	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)[64,]	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)[69,]		*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*			

Study			Low-Risk		Intermediate-Risk		High-Risk	
		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)
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.[68,] 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).[39,]

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
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).[65,] 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 ($p<.001$) in prognostic information. Filipits et al (2019) reported longer follow-up of the cohort from the ABCSG-6 and ABCSG-8 trials.[54,] 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).[39,]

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.

Incorporating the BCI as a continuous variable, Zhang et al (2013) developed an "optimized model" to predict early and late distant recurrences.[44,] 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.[43,] 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][44,]), 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)[73,] 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 24. 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)[73,]	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.

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

Four studies using data from patients randomized in previous trials have examined the ability of the Breast Cancer Index to predict likelihood of benefit from extended endocrine therapy (Table 23). Three of the studies included a mix of patients with node-positive and node-negative breast cancer. Results were similar across studies and in subsets of women with node-positive breast cancer.[70,44,71,72,]

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.[70,] 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 versus 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 25).[44,]

Final results of the ATToM trial were reported by Bartlett et al (2022).[74,]

Noordhoek et al (2021) evaluated the BCI H/I ratio assay in participants from the IDEAL trial, an RCT comparing 2.5 versus 5 years of extended letrozole.[72,]

Table 25. 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)[70,]	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)[44,]	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
Bartlett et al (2019)[71,] Bartlett et al (2022)[74,]	583	10 vs. 5 years of tamoxifen	1.07 (0.69 to 1.65)	-0.2 %	0.35 (0.15 to 0.86)	10.2 %	Prospective-retrospective study in patients previously randomized in the aTTom, trial
Noordhoek et al (2021)[72,]	908 (664 node-positive)	2.5 vs. 5 years of extended letrozole	0.95 (0.58 to 1.56); p=.84 Node positive subset: 0.88 (0.50		0.42 (0.21 to 0.84); p=.011 Node positive subset:	node positive subset: 10.8 %	Prospective-retrospective study in patients previously randomized in the IDEAL trial

Study	N	Comparators	Low-Risk		High-Risk		Note
			to 1.53); p=.644		0.30 (0.12 to 0.77)		

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

Four 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)

Esserman et al (2017) conducted a secondary analysis of data from women who were node-negative, participating in an RCT of tamoxifen versus no systemic therapy, with over 20 years of follow-up, the STO-3 trial, (see Table 20).[69,] 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<.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.[75,]

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

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

Sestak et al (2013) reported limited results concerning late recurrences obtained from patients in the ATAC trial who received anastrozole with tamoxifen alone or in combination.[68,] 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)[67,] combined samples of women with hormone receptor-positive, *HER2*-negative cancers from the ABCSG-8 and TransATAC studies included in the 2 prior publications.[66,68,] 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 26. Classification and Reclassification Achieved by Adding ROR Score to the CTS

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

Distant Recurrence		***CTS***					***CTS***			
	Total	1106	631	252	1989		1106	631	252	1989

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

Limitations (eg, 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.

Table 27. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of FU[e]
Dubsky et al (2013)[65,]	4. Includes both node-negative and -positive patients			4. Reclassification of diagnostic or risk categories not reported	
Sestak et al (2013)[68,]	4. Includes both node-negative and -positive patients			4. Reclassification of diagnostic or risk categories not reported	
Sgroi et al (2013)[43,]	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)[70,]	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)[44,]				4. Reclassification of diagnostic or risk categories not reported	
Filipits et al (2014)[66,]	4. Includes both node-negative and -positive patients			4. Reclassification of diagnostic or risk categories not reported	
Esserman et al (2017)[69,]	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		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	

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of FU[e]
	some *HER2*-negative				
Sestak et al (2015)[67,]	4. Includes both node-negative and -positive patients				
Sestak et al (2018)[39,]	4. Includes both node-negative and -positive patients			4. Reclassification of diagnostic or risk categories not reported	
Bartlett et al (2019)[71,]			3. No comparator (standard of care is clinical risk indicators)	1.Incremental improvement in applying risk category over standard is lacking	
Noordhoek et al (2021)[72,]	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	

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 28. 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)[65,]	2. Sample of women from another study					
Sestak et al (2013)[68,]	2. Sample of women from another study					
Sgroi et al (2013)[43,]	2.Sample of women from another study					

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Sgroi et al (2013)[70,]	2. Sample of women from another study					
Zhang et al (2013)[44,]	2. Sample of women from another study					
Filipits et al (2014)[66,]	2. Sample of women from another study					
Esserman et al (2017)[69,]	2. Sample of women from another study					
Sestak et al (2018)[39,]	2.Sample of women from another study					
Bartlett et al (2019)[71,]	2.Sample of women from another study					
Noordhoek et al (2021)[72,]	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.[12,] 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. Aromatase inhibitors have increased cardiovascular and musculoskeletal adverse events compared with tamoxifen.

In addition, noncompliance rates in women taking endocrine therapy are as high as 30%.[76,]

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 for any test. 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[6,] 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.

Insight TNBCtype Test
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.

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.[77,78,] 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.

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.

Section Summary: Triple-Negative Breast Cancer Considering Neoadjuvant Chemotherapy
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.

MULTIPLE ASSAYS OF GENETIC EXPRESSION IN TUMOR TISSUE PERFORMED ON THE SAME INDIVIDUAL WITH BREAST CANCER TO DETERMINE PROGNOSIS

Clinical Context and Therapy Purpose
The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with breast cancer.

Interventions
The interventions being considered are repeat gene expression profile testing using the same test or a combination of tests on the same individual.

Comparators
The comparator of interest is testing using a single assay to determine prognosis.

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.

REVIEW OF EVIDENCE

Repeat Testing With the Same Assay
Marumoto et al (2021) used data from a prospectively maintained pathology database to identify individuals with 2 or more Oncotype DX RS from multiple ipsilateral primary breast tumors, contralateral tumors, in-breast recurrent tumors, or breast tumors undergoing repeat genomic testing.[79,] RS concordance was 100% in the same tumor, 91.7% in multiple ipsilateral tumors, 71.4% in contralateral tumors, and 66.7% in in-breast recurrent tumors. Toole et al. reported that 22% (4 out of 18) had Oncotype Dx score differences that led to changes in management but did not report clinical outcomes.[80,] Additionally though, Toole, et al. found that in a small number of cases the histology and grade were the same on ipsilateral lesions yet had significantly different Oncotype Dx scores altering chemotherapy recommendations.

Testing with a Combination of Assays
Several studies were identified that compared the performance of different assays tested on the same samples (e.g., Espinosa et al [2005][81,]; Sestack et al [2016, 2018][82,39,]; Sgroi et al [2013][43,]), but these studies were not designed to evaluate a strategy of repeat or combination testing in the same individual and are not discussed further.

Section Summary: Multiple Assays of Genetic Expression in Tumor Tissue Performed on the Same Individual with Breast Cancer to Determine Prognosis
There are no studies directly comparing a strategy of repeat or combination testing compared to using a single assay. Additionally, evidence-based clinical practice guidelines recommend against a strategy of repeat testing. NCCN breast cancer treatment guidelines (v.4.2022) state, "Since results of different assays may not be concordant with each other and these assays have not been compared head-to-head prospectively, clinicians should only order one of the available assays for a specific patient and tumor."[3,] In its 2020 guidance intended for community

oncologists, the Breast Cancer Therapy Expert Group (BCTEG) noted "Discordance between available genomic tests is expected because the different tests were developed and validated across a range of patient populations and treatment backgrounds; performing more than one genomic test on a patient should be avoided, as uncertainties in risk assignment may result."[83,]

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 an 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 an 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 an 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%-96%), but not as high survival for the low-risk group not treated with tamoxifen (83%, 95% CI, 76%-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 an 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 an 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 a clinical utility study demonstrating that postmenopausal women with a RS score of 0 to 25 could safely forego adjuvant chemotherapy without compromising invasive disease–free survival or distant relapse–free survival. In the RxPONDER trial, participants (N = 5083) with hormone-receptor–positive, HER2-negative breast cancer, 1 to 3 positive axillary lymph nodes, and a RS of 25 or lower were randomized to endocrine therapy only or to chemotherapy plus endocrine (chemoendocrine) therapy. Among postmenopausal women (66.8%), estimates of invasive disease–free survival at 5 years were 91.3% in the chemoendocrine group and 91.9% in the endocrine-only group (hazard ratio for invasive disease recurrence, new primary cancer [breast cancer or another type], or death, 1.02; 95% CI, 0.82 to 1.26; P =.89). In premenopausal women, the rate of invasive disease–free survival at 5 years among those in the chemoendocrine group was 93.9%, as compared with 89.0% among those in the endocrine-only group (absolute difference, 4.9 percentage points), with a significant chemotherapy benefit (hazard ratio for invasive disease recurrence, new primary cancer [breast cancer or another type], or death, 0.60; 95% CI, 0.43 to 0.83; P =.002). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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 that the technology results in an improvement in the net health outcome.

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 an 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 that the technology results in an improvement in the net health outcome.

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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 that the technology results in an improvement in the net health outcome.

DCISionRT
For individuals who have DCIS considering radiotherapy who receive gene expression profiling with DCISionRT, the evidence includes retrospective validation studies. One Simon et al (2009) category B study provided evidence for clinical validity which showed no benefit of radiation therapy among a group of participants classified as low risk using the DCIS RT score at a threshold of <3 (absolute risk difference for invasive recurrence 1.2% (-5.7% to 8.2%). However, it is unclear whether the estimated 10-year recurrence risk for this group (12.4%; 95% CI 7.2% to 20.8% for invasive recurrence) is low enough to consider changing management or is estimated with sufficient precision. 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).The evidence is insufficient to determine that the technology results in an improvement in the net health outcome

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 that the technology results in an improvement in the net health outcome.

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 to 10 years (5.9%; 95% CI, 2.2% to 9.5%) and at 5 to 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 one 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 that the technology results in an improvement in the net health outcome.

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 that the technology results in an improvement in the net health outcome.

For individuals who have early-stage node-positive (1 to 5 nodes) invasive breast cancer who are distant recurrence-free at 5 years who are considering extending endocrine treatment who receive gene expression profiling with the Breast Cancer Index, the evidence includes 4 analyses of archived tissue samples from previously conducted clinical trials. The analyses showed low distant recurrence rates and high distant recurrence-free survival rates in patients classified as low-risk with the test. The 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 that the technology results in an improvement in the net health outcome.

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 that the technology results in an improvement in the net health outcome.

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 that the technology results in an improvement in the net health outcome.

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 that the technology results in an improvement in the net health outcome.

Repeat Testing
For individuals with breast cancer who receive multiple (repeat) assays of genetic expression in tumor tissue to determine prognosis, the evidence includes studies comparing different tests in groups of individuals but no direct evidence evaluating repeat testing with the same test or a combination of tests performed on the same individual. Additionally, clinical practice guidelines recommend against a strategy of repeat testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society of Clinical Oncology
In June 2022, the American Society of Clinical Oncology (ASCO) published updated clinical practice guidelines on the use of breast cancer biomarker assay results to guide adjuvant endocrine and chemotherapy decisions in early-stage breast cancer. The recommendations related to the interventions and populations included in this evidence opinion are listed in Table 29.[84,]

The guidelines do not address the use of assays such as Oncotype DCIS or DCISionRT to guide decisions about radiation therapy in individuals with DCIS.

Table 29. American Society of Clinical Oncology Guidelines on the Use of Biomarker Assays to Guide Adjuvant Endocrine and Chemotherapy Decisions in Early-Stage Breast Cancer- 2022

Interventions	Recommendation	Evidence Quality	Strength of Recommendation
Newly Diagnosed ER-Positive, HER2-Negative Breast Cancer			
Oncotype DX (21-generecurrence	1.1. If a patient has node-negative breast cancer, the clinician may use Oncotype DX test to guide decisions for adjuvant endocrine and chemotherapy	High	Strong

Interventions	Recommendation	Evidence Quality	Strength of Recommendation
Newly Diagnosed ER-Positive, HER2-Negative Breast Cancer			
score, 21-gene RS)	1.2. In the group of patients in Recommendation 1.1 with Oncotype DX score greater than or equal to 26, the clinician should offer chemoendocrine therapy	High	Strong
	1.3. In the group of patients in Recommendation 1.1 who are 50 years of age or younger with Oncotype DX score 16 to 25, the clinician may offer chemoendocrine therapy	Intermediate	Moderate
	1.4. If a patient is postmenopausal and has node-positive breast cancer with 1-3 positive nodes, the clinician may use Oncotype DX test to guide decisions for adjuvant endocrine and chemotherapy	High	Strong
	1.5. In the group of patients in Recommendation 1.4, the clinician should offer chemoendocrine therapy for those whose Oncotype DX score is greater than or equal to 26	High	Strong
	1.6. If a patient is premenopausal and has node-positive breast cancer with 1-3 positive nodes, Oncotype DX test should not be offered to guide decisions for adjuvant systemic chemotherapy	High	Moderate
	*Qualifying statement:*The genomic assay is prognostic and may be used for shared patient-physician treatment decision making		
	1.7. If a patient has node-positive breast cancer with more than 3 positive nodes, the evidence on the clinical utility of routine Oncotype DX test to guide decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use	Insufficient	Moderate
MammaPrint (70-genesignature)	1.8. If a patient is older than 50 and has high clinical risk breast cancer, that is node-negative or node-positive with 1-3 positive nodes, the clinician may use MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy	Intermediate	Strong
	1.9. If a patient is 50 years of age or younger and has high clinical risk, node negative or node-positive with 1-3 positive nodes breast cancer, the clinician should not use the MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy	High	Strong
	1.10. If a patient has low clinical risk, regardless of age, the evidence on clinical utility of routine MammaPrint test is insufficient to recommend its use	Intermediate	Moderate
	1.11. If a patient has node-positive breast cancer with more than 3 positive nodes, the evidence on	Insufficient	Strong

Interventions	Recommendation	Evidence Quality	Strength of Recommendation
Newly Diagnosed ER-Positive, HER2-Negative Breast Cancer			
	the clinical utility of routine MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use		
	*Qualifying statement:*The genomic assay is prognostic and may be used for shared patient-physician treatment decision making		
EndoPredict (12-generisk score)	1.12. If a patient is postmenopausal and has breast cancer that is node negative or node-positive with 1-3 positive nodes, the clinician may use EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy	Intermediate	Moderate
	1.13. If a patient is premenopausal and has breast cancer that is node negative or node-positive with 1-3 positive nodes, the clinician should not use EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy	Insufficient	Moderate
	1.14. If a patient has breast cancer with more than 3 positive nodes, evidence on the clinical utility of routine use of EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy is insufficient	Intermediate	Moderate
Prosigna (PAM50)	1.15. If a patient is postmenopausal and has breast cancer that is node negative, the clinician may use the Prosigna test to guide decisions for adjuvant systemic chemotherapy	Intermediate	Moderate
	1.16. If a patient is premenopausal, and has node-negative or node-positive breast cancer the clinician should not use the Prosigna test to guide decisions for adjuvant systemic chemotherapy	Insufficient	Moderate
	1.17. If a patient is postmenopausal and has node-positive breast cancer with 1-3 positive nodes, the evidence is inconclusive to recommend the use of Prosigna test to guide decisions for adjuvant endocrine and chemotherapy	Intermediate	Moderate
	1.18. If a patient has node-positive breast cancer with more than 3 positive nodes, evidence on the clinical utility of routine use of Prosigna test to guide decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use	Insufficient	Strong
Extended Endocrine Therapy for ER Receptor-Positive HER2-Negative Breast Cancer			
Oncotype DX,EndoPredict, Prosigna	1.23. If a patient has node-negative breast cancer and has had 5 years of endocrine therapy without evidence of recurrence, there is insufficient evidence to use Oncotype DX, EndoPredict,	Intermediate	Moderate

Interventions	Recommendation	Evidence Quality	Strength of Recommendation
Newly Diagnosed ER-Positive, HER2-Negative Breast Cancer			
	Prosigna, Ki67, or IHC4 tests to guide decisions about extended endocrine therapy		
Breast Cancer Index(BCI)	1.24. If a patient has node-negative or node-positive with 1-3 positive nodes breast cancer and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, the clinician may offer BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI or a sequence of tamoxifen followed by AI	Intermediate	Moderate
	1.25. If a patient has node-positive breast cancer with more than 3 positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, there is insufficient evidence to use BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI or a sequence of tamoxifen followed by AI	Intermediate	Strong
HER2-Positive Breast Cancer or Triple-Negative Breast Cancer			
Oncotype DX,EndoPredict, MammaPrint, BCI,Prosigna,	1.27. If a patient has HER2-positive breast cancer or TNBC, the clinician should not use multiparameter gene expression or protein assays (Oncotype DX, EndoPredict, MammaPrint, BCI, Prosigna, Ki67, or IHC4) to guide decisions for adjuvant endocrine and chemotherapy	Insufficient	Strong

Source: adapted from Andre et al (2022) Summary of Recommendations Table (Data Supplement)[84,]

Breast Cancer Therapy Expert Group

In 2020, the Breast Cancer Therapy Expert Group (BCTEG) published guidance on the use of genomic testing in early breast cancer. [83,]The guidance was intended for community oncologists and included the following clinical practice points:

- "Genomic testing is generally only indicated in patients with hormone receptor-positive and HER2 negative tumors, and those with up to 3 positive nodes.
- Genomic testing should generally not be performed for patients with hormone receptor negative disease, > 3 positive nodes, HER2 positivity, or TNBC outside the context of a clinical trial.
- Genomic testing should generally not be performed in patients for whom the results of the testing will not affect the course of treatment.
- Importantly, neither ASCO nor NCCN guidelines currently imply the superiority of any one genomic test over another.
- Discordance between available genomic tests is expected because the different tests were developed and validated across a range of patient populations and treatment backgrounds; performing more than one genomic test on a patient should be avoided, as uncertainties in risk assignment may result."

National Comprehensive Cancer Network

The current NCCN guidelines for breast cancer are Version 4.2022.[3,] Guidelines are updated frequently; refer to the source for most recent guidelines. Recommendations related to the interventions and populations included in this evidence opinion, current as of September 13, 2022, are listed in Table 30.[84,]

The guidelines state, "Since results of different assays may not be concordant with each other and these assays have not been compared head-to-head prospectively, clinicians should only order one of the available assays for a specific patient and tumor."

The guidelines do not address the use of assays such as Oncotype DCIS or DCISionRT to guide decisions about radiation therapy in individuals with DCIS.

Table 30. National Comprehensive Cancer Network Recommendations on the Use of Biomarker Assays to Guide Adjuvant Endocrine and Chemotherapy Decisions in Early-Stage Breast Cancer

Assay	Population	NCCN Category of Preference	NCCN Category of Evidence
Gene Expression Assays for Consideration of Adjuvant Systemic Therapy			
21-gene (Oncotype Dx)	Node negative	Preferred	1
	1-3 positive nodes, postmenopausal	Preferred	1
	1-3 positive nodes, premenopausal	Other	2A
70-gene (MammaPrint)	Node negative	Other	1
	1-3 positive nodes	Other	1
50-gene (Prosigna)	Node negative	Other	2A
	1-3 positive nodes	Other	2A
12-gene (EndoPredict)	Node negative	Other	2A
	1-3 positive nodes	Other	2A
Gene Expression Assays for Consideration of Adjuvant Systemic Therapy			
Breast Cancer Index (BCI)		Other	2A

Source: [3,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Current ongoing and unpublished trials that might influence this review are listed in Table 31.

Table 31. 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	Oct 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 2023
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	672	Jun 2026
NCT02889874	A Randomized Phase III Trial of Adjuvant Radiation Therapy Versus Observation Following Breast Conserving Surgery and Endocrine Therapy in Patients With Molecularly Characterized Luminal A Early Breast Cancer	1167	Dec 2023
NCT02400190	The IDEA Study (Individualized Decisions for Endocrine Therapy Alone)	202	Mar 2026
NCT03503799	Prospective Assessment of Disease Progression in Primary Breast Cancer Patients Undergoing EndoPredict Gene Expression Testing - a Care Research Study	1191	Oct 2032
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	1278	Jun 2030
ISRCTN42400492	Optimal personalized 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
NCT04852887	A Phase III Clinical Trial Evaluating De-Escalation of Breast Radiation for Conservative Treatment of Stage I,	1670	Jul 2041

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Hormone Sensitive, HER-2 Negative, Oncotype Recurrence Score Less Than or Equal to 18 Breast Cancer		
NCT02476786	Endocrine Treatment Alone as Primary Treatment for Elderly Patients With Estrogen Receptor Positive Operable Breast Cancer and Low Recurrence Score	50	Jan 2030
NCT03917082	Single arm phase II study exploring reducing the duration of endocrine therapy from five to two years in low risk population with early breast cancer	290	May 2029

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

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
81518	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy
81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score
81520	Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping) utilizing formalin-fixed paraffin-embedded tissue, algorithm reporting as a recurrence risk score
81521	Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis
81522	Oncology (breast), mRNA gene expression profiling
81523	Oncology, mRNA, next-generation sequencing gene expression profiling (effective 01-01-22)
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
0295U	Oncology (breast ductal carcinoma in situ), protein expression profiling by immunohistochemistry of 7 proteins (COX2, FOXA1, HER2, Ki-67, p16, PR, SIAH2), with 4 clinicopathologic factors (size, age, margin status, palpability), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a recurrence risk score
S3854	Gene expression profiling panel for use in the management of breast cancer treatment

ICD-10 DIAGNOSES	
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.021	Malignant neoplasm of nipple and areola, right male breast
C50.022	Malignant neoplasm of nipple and areola, left male breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
D05.00	Lobular carcinoma in situ of unspecified breast
D05.01	Lobular carcinoma in situ of right breast
D05.02	Lobular carcinoma in situ of left breast
D05.10	Intraductal carcinoma in situ of unspecified breast
D05.11	Intraductal carcinoma of situ of right breast
D05.12	Intraductal carcinoma in situ of left breast
D05.80	Other specified type of carcinoma in situ of unspecified breast
D05.81	Other specified type of carcinoma in situ of right breast
D05.82	Other specified type of carcinoma in situ of left breast
D05.90	Unspecified type of carcinoma in situ of unspecified breast
D05.91	Unspecified type of carcinoma in situ of right breast
D05.92	Unspecified type of carcinoma in situ of left breast
Z17.0	Estrogen receptor positive status [ER+]

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

REVISIONS	
	In the Policy Guidelines section: • Added the following: "According to the American Society of Clinical Oncology-College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer, "a positive HER2 result is IHC [immunohistochemistry] staining of 3+ (uniform, intense membrane staining of >30% of invasive tumor cells), a fluorescent in situ hybridization (FISH) result of more than six HER2 gene copies per nucleus or a FISH ratio (HER2 gene signals to chromosome 17 signals) of more than 2.2; a negative result is an IHC staining of 0 or 1+, a FISH result of less than 4.0 HER2 gene copies per nucleus, or FISH ratio of less than 1.8. Equivocal results require additional action for final determination." (1)"
	Updated the Rationale section.
	Updated the Reference section.
04-12-2013	Updated Description section.
	In Policy section: ▪ In Item D, revised the following "patients who are lymph node positive" to read "patients with positive lymph nodes". ▪ In Item D, inserted "or patient with bilateral disease" to read "patients with positive lymph nodes or patient with bilateral disease," ▪ Added Item E, "Use of a subset of genes from the 21-gene RT-PCR assay for predicting recurrence risk in patients with noninvasive ductal carcinoma in situ (i.e., Oncotype DX DCIS) to inform treatment planning following excisional surgery is considered experimental / investigational." ▪ In Item F, revised the following "The use of other gene expression assays (e.g., MammaPrint, Mammostrat, or the THEROS Breast Cancer Index^{SM}) for any indication is considered experimental / investigational." to read "The use of other gene expression assays (e.g., MammaPrint, Mammostrat Breast Cancer Test, the Breast Cancer Index, The BreastOncPx, NexCourse Breast IHC4, or PAM50 Breast Cancer Intrinsic Classifier) for any indication is considered experimental / investigational."
	Updated Rationale section.
	In Coding section: ▪ Added diagnosis code, 233.0
	Updated Reference section.
03-27-2014	Updated Description section.
	In Policy section: ▪ Added new Item D, "The use of gene expression assays in men with breast cancer is considered medically necessary. ▪ In Item G, added "Breast PRS and EndoPredict" to read "…or PAM50 Breast Cancer Intrinsic Classifier, Breast PRS and EndoPredict) for any indication is considered experimental / investigational." ▪ Added Item H, "The use of gene expressional assays to molecularly subclassify breast cancer (e.g., BluePrint) is considered experimental / investigational." ▪ Added Item I, "The use of gene expression assays for quantitative assessments of ER, PR, and HER2 overexpression (e.g., TargetPrint) is considered experimental / investigational."
	Updated Rationale section.
	In Coding section: ▪ Added ICD-10 Diagnosis *(Effective October 1, 2014)*
	Updated Reference section.
01-01-2015	Policy posted 01-16-2015

REVISIONS	
	In Coding section: ▪ Added CPT Codes: 81519 (Effective January 1, 2015), 0008M (Effective July 1, 2014) ▪ Added CPT Code: 84999 (applies to applicable services before January 1, 2015)
04-28-2015	Title of Policy changed from "Gene Expression Assay for Breast Cancer Treatment."
	Updated Description section.
	In Policy section: ▪ In Item A, added "invasive" and "all of", to read, "The use of the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (i.e., Oncotype DX®) to determine recurrence risk for deciding whether or not to undergo adjuvant chemotherapy may be considered medically necessary in women with primary, invasive breast cancer meeting all of the following characteristics:" ▪ In Item E, added "invasive", to read, "All other indications for the 21-gene RT-PCR assay (i.e., Oncotype DX®), including determination of recurrence risk in invasive breast cancer patients with positive lymph nodes or patient with bilateral disease, are considered experimental / investigational." ▪ In Item G, added "70-gene signature" and "Prosigna™" and removed "or PAM50 Breast Cancer Intrinsic Classifier," to read, "The use of other gene expression assays (e.g., MammaPrint® 70-gene signature, Mammostrat® Breast Cancer Test, the Breast Cancer Index℠, the BreastOncPx™, NexCourse® Breast IHC4, Prosigna™, BreastPRS™, and EndoPredict™) for any indication is considered experimental / investigational." In Policy Guideline section: ▪ In Item 1, added "0.6" and removed "0.3", to read, "Unfavorable features that may prompt testing in tumors from 0.6 to 1 cm in size include the following: angiolymphatic invasion, high histologic grade, or high nuclear grade." ▪ In Item 3, removed, "a positive HER2 result is IHC [immunohistochemistry] staining of 3+ (uniform, intense membrane staining of >30% of invasive tumor cells), a fluorescent in situ hybridization (FISH) result of more than six HER2 gene copies per nucleus or a FISH ratio (HER2 gene signals to chromosome 17 signals) of more than 2.2; a negative result is an IHC staining of 0 or 1+, a FISH result of less than 4.0 HER2 gene copies per nucleus, or FISH ratio of less than 1.8. Equivocal results require additional action for final determination.(1)" and added ",(1) defines positive, negative, and equivocal HER2 test results as shown in table 2", to read, "According to the American Society of Clinical Oncology-College of American Pathologists G guideline, "Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer,"(1) defines positive, negative, and equivocal HER2 test results as shown in Table 2." ▪ Added Table 2
	Updated Rationale section.
	In Coding section: ▪ Removed " There are no specific CPT codes for these laboratory tests. Effective 1/1/06, an S code was designated for this test: S3854," and added, "Effective 07/01/14, there is a CPT multianalyte assay with algorithmic analysis (MAAA) administrative code specific to the Prosigna test: 0008M. Effective January 1, 2015, there is a specific CPT MAAA code for Oncotype DX: 81519. Effective January 1, 2006, an S code was designated for this test: S3854. The other tests mentioned above would be reported with an unlisted CPT code such as 81599."
	Updated References section.
09-29-2015	Updated Description section.
	In Policy section:

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	▪ In Item A, removed "or not", to read "The use of the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (i.e., Oncotype DX®) to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy may be considered medically necessary in women with primary, invasive breast cancer meeting ALL of the following characteristics:" ▪ In Item A 1, removed "non-fixed", to read "unilateral tumor; AND" In Policy Guidelines: ▪ In Item 3, removed "According to the", and added "The current (2013)", to read "The current (2013) American Society of Clinical Oncology-College of American Pathologists guideline…"
	Updated Rationale section.
	Updated References section.
01-01-2016	In Coding section: ▪ Removed HCPCS code S3854.
07-01-2016	In Coding section: ▪ Added HCPCS code S3854. ▪ Revising coding bullets.
01-04-2017	Updated Description section.
	In Policy section: ▪ In Item A, added "Endopredict, the Breast Cancer Index℠, and Prosigna" to read, "The use of the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (i.e., Oncotype DX®), EndoPredict, the Breast Cancer IndexSM, and Prosigna to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy may be considered medically necessary in women with primary, invasive breast cancer meeting ALL of the following characteristics:" ▪ In Item F, added "All other indications for the 21-gene RT-PCR", "(i.e., Oncotype DX®)", and "including determination of recurrence risk in invasive breast cancer patients with positive lymph nodes, patients with bilateral disease, or to consider length of treatment with tamoxifen, are" and removed "The use of other gene expression", "e.g., MammaPrint® 70-gene signature, Mammostrat® Breast Cancer Test,", "the BreastOncPx™, NexCourse® Breast IHC4,", "Breast PRS™", and "for any indication is" to read, "All other indications for the 21-gene RT-PCR assay (i.e., Oncytope DX®), Endopredict™, the Breast Cancer Index℠, and Prosigna®, including determination of recurrence risk in invasive breast cancer patients with positive lymph nodes, patients with bilateral disease, or to consider length of treatment with tamoxifen, are considered experimental / investigational." ▪ In Item G, added "Breast" and "Score" to read, "Use of a subset of genes from the 21-gene RT-PCR assay for predicting recurrence risk in patients with noninvasive ductal carcinoma in situ (i.e., Oncotype DX® Breast DCIS Score) to inform treatment planning following excisional surgery is considered experimental / investigational." ▪ Added new Item H, "Use of 70-gene signature (MammaPrint®) for any indication is considered experimental / investigational." ▪ In new Item I (previous Item H), added "in conjunction with MammaPrint® or alone" and removed "gene expression assays to molecularly subclassify breast cancer (e.g.," to read, "The use of BluePrint® in conjunction with MammaPrint® or alone is considered experimental / investigational." ▪ Removed previous Item I, "The use of gene expression assays for quantitative assessment of ER, PR, and HER2 overexpression (e.g., TargetPrint®) is considered experimental / investigational."
	Updated Rationale section.

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	In Coding section: ▪ Added CPT code: 81599. ▪ Removed CPT code: 84999. ▪ Updated coding bullets.
	Updated References section.
	Added Appendix section.
10-28-2017	Updated Description section.
	In Policy section: ▪ In Item A, removed "women" and added "individuals" to read, "The use of the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (i.e., Oncotype DX®), EndoPredict, the Breast Cancer Index, and Prosigna to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy may be considered medically necessary in individuals with primary, invasive breast cancer meeting ALL of the following characteristics:" ▪ Removed Item D, "The use of gene expression assays in men with breast cancer is considered medically necessary."
	Updated Rationale section.
	In Coding section: ▪ Updated coding bullets.
	Updated References section.
01-01-2018	Updated Description section.
	In Policy section: ▪ Removed Item D, "All other indications for the 21-gene RT-PCR assay (i.e., Oncotype DX), including determination of recurrence risk in invasive breast cancer patients with positive lymph nodes or patients with bilateral disease, are considered experimental / investigational."
	Updated Rationale section.
	In Coding section: ▪ Added CPT codes: 81520, 81521. ▪ Removed coding bullets. ▪ Removed ICD-9 codes.
	Updated References section.
08-01-2018	Updated Rationale section.
	Updated References section.
01-01-2019	In Coding section: ▪ Added new CPT code: 81518
02-01-2019	Policy published 01-04-2019 with an effective date of 02-01-2019.
	Updated Description section.
	In Policy section: ▪ In Item A, added "MammaPrint" and removed "the 21-gene reverse transcriptase-pomymerase chain reaction (RT-PCR) assay" to read, "The use of Oncotype DX, EndoPredict, the Breast Cancer Index, MammaPrint, and Prosigna to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy may be considered medically necessary in individuals with primary, invasive breast cancer meeting ALL of the following characteristics:" ▪ In Item D, added "MammaPrint" and removed "the 21-gene RT-PCR assay" to read, "All other indications for Oncotype DX, EndoPredict, the Breast Cancer Index, MammaPrint, and Prosigna, including determination of recurrence risk in invasive breast cancer patients with positive lymph nodes, patients with bilateral disease, or

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	to consider length of treatment with tamoxifen, are considered experimental / investigational." ▪ Removed previous Item F, "Use of 70-gene signature (MammaPrint) for any indication is considered experimental / investigational." ▪ Removed Policy Guidelines.
	Updated Rationale section.
	Updated References section.
	Removed Appendix section.
07-17-2019	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Added CPT code: 0045U. ▪ Deleted termed CPT code: 0008M. *(Effective January 1, 2018)*
	Updated References section.
01-01-2020	In Coding section: ▪ Added CPT Code: 81522
03-29-2021	Updated Description section
	In Policy Section • Item A: Added "women" and deleted "individuals" • Item A 2: Deleted "ER" and "PR" • Item A 3: Deleted "HERS" • Item A 4: Deleted conduct testing on • Item 5: Added "for 21 gene RT-PCR assay" • Item 8 Added: "The use of Insight TNBCtype to aid in making decisions regarding chemotherapy in women with triple-negative breast cancer is considered experimental / investigational."
	Updated Rationale section
	In Coding Section • Removed CPT code 81599 • Added ICD-10 Codes: D05.00, D05.01, D05.02, D05.10, D05.11, D05.12, D05.80, D05.81, D05.90, D05.91, D05.92
	Updated Reference section
01-04-2022	Updated Description Section
	Updated Policy Section: • Section F: changed "tamoxifen" to "endocrine therapy"
	In Coding section: Added CPT 81523 (effective 01-01-22), 0295U(effective 01-01-22), 0153U Added ICD-10 code Z17.0
	Update Rationale Section
	Updated References Section
	Added Appendix Section
02-09-2023	Updated Description Section
	Updated Policy Section: ▪ Section A Added: "EndoPredict, the Breast Cancer Index, MammaPrint, or Prosigna" and "node-negative" ▪ Section B Removed: "Use of EndoPredict, the Breast Cancer Index, MammaPrint, and Prosigna to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy may be considered medically necessary in women with primary, invasive breast cancer with the same characteristics as considered medically necessary for Oncotype DX." ▪ Section C Added: " node-positive"

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	▪ Section C Added C6: "no distant metastases; AND" ▪ Section C Added C8: "eligible for a chemotherapy regimen containing a taxane, an anthracycline, or both; AND" ▪ Added Section D: "The use of Oncotype Dx to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy may be considered medically necessary in women with primary, invasive, node positive breast cancer meeting ALL of the following characteristics: 1. postmenopausal (defined as previous bilateral oophorectomy or more than 12 months since the last menstrual period and no previous hysterectomy); 2. unilateral tumor; AND 3. hormone receptor-positive (ie, estrogen receptor-positive or progesterone receptor-positive); AND 4. human epidermal growth factor receptor 2-negative; AND 5. stage T1 or T2 or operable T3 at high clinical risk (see Policy Guidelines); AND 6. 1 to 3 positive nodes (N1); AND 7. no distant metastases; AND 8. who will be treated with adjuvant endocrine therapy (eg, tamoxifen, aromatase inhibitors); AND 9. eligible for a chemotherapy regimen containing a taxane, an anthracycline, or both; AND 10. when the test result aids the patient in deciding on chemotherapy (ie, when chemotherapy is a therapeutic option); AND 11. when ordered within 6 months after diagnosis, because the value of the test for making decisions regarding delayed chemotherapy is unknown. ▪ Added Section E: "The use of Oncotype Dx to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy in premenopausal women (defined as less than 6 months since the last menstrual period) with primary, invasive, node positive breast cancer is considered experimental / investigational (see Policy Guidelines)." ▪ Added Section F: "The use of EndoPredict, the Breast Cancer Index, and Prosigna to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy in individuals with primary, invasive, node positive breast cancer is considered experimental / investigational." ▪ Section I Removed: "determination of recurrence risk in invasive breast cancer patients with positive lymph nodes, patients with bilateral disease, or" and Added "repeat testing with same test, or combination testing with various tests" ▪ Added Section K: "Use of the DCISion RT assay for predicting recurrence risk in individuals with noninvasive ductal carcinoma in situ to inform treatment planning after excisional surgery is considered experimental / investigational."
	Updated Policy Guidelines ▪ Added Sections A, B, Title to C, and D A. Unilateral Bilateral Premenopausal Most breast cancer is unilateral, occurring in one breast. Bilateral breast cancer, breast cancer in both breasts, can be synchronous or metachronous. Synchronous is generally defined as occurring within 6 months, but other intervals are used (3 months or even 12 months), and overall, inconsistency in the use of the term "bilateral breast cancer" occurs. It is difficult to clearly know if a second breast cancer appearing within months of the first is metastatic spread or a new primary. There are no professional guidelines on use of gene expression assays in bilateral breast cancers, although small studies show Oncotype Dx score discordancy in synchronous bilateral ER-positive HER2-negative breast cancer with associated chemotherapy recommendation changes of 50% to 57%. No health outcomes were reported from the change in chemotherapy recommendations. As such, the position relates only to unilateral breast cancer although at the local level consideration could be given to genetic expression assay in a second cancer in the contralateral breast. B. Premenopausal The position on premenopausal women with node positive breast cancer differs from the NCCN guidelines (https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf). The NCCN guidelines have a 2A recommendation for OncotypeDx testing of premenopausal women with 1-3 positive lymph nodes based on the RxPONDER trial (Kalinsky et. al., 2021; PMID 34914339). Based on this test, the NCCN guidelines have a recommendation to "consider chemotherapy followed by endocrine therapy or alternatively, ovarian function suppression combined with either

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	tamoxifen or an Aromatase inhibitor." Note that RxPONDER was not designed to test whether chemotherapy can be replaced by ovarian suppression, and that among premenopausal women, invasive disease–free survival at 5 years was 89.0% with endocrine-only therapy and 93.9% with chemoendocrine therapy (hazard ratio, 0.60; 95% CI, 0.43 to 0.83; P = 0.002), with a similar increase in distant relapse–free survival (hazard ratio, 0.58; 95% CI, 0.39 to 0.87; P = 0.009) indicating benefit of chemoendocrine therapy. While the evidence then is insufficient to support Oncotype DX testing as perhaps all premenopausal women benefit from chemoendocrine therapy regardless of Oncotype DX recurrence score, with the NCCN 2A recommendation for using Oncotype Dx testing for premenopausal women a local decision might need to be made. C. Clinical Risk D. Multiple Ipsilateral Tumors Gene expression assay testing on multiple ipsilateral primary tumors could start with assessing the most histologically aggressive, as concordance of Oncotype Dx score with Nottingham score is strong. However, a low Oncotype Dx score indicating no need for adjuvant chemotherapy from the most aggressive appearing tumor might not negate the need for Oncotype Dx testing of other primary tumors. The literature base for this strategy is slim; but, for ipsilateral multiple tumors, Toole, et al. show that 22% (4 out of 18) had Oncotype Dx score differences that led to changes in management. Additionally though, Toole, et al. found that in a small number of cases the histology and grade were the same on ipsilateral lesions yet had significantly different Oncotype Dx scores altering chemotherapy recommendations. Larger, prospective studies are needed including clinical outcomes from management changes. Consideration at the local level could be given to histologically distinct tumors meeting the other criteria for gene expression assay testing, or serial testing. There is no literature assessing the use of one gene expression assay on one tumor and a different gene expression assay on another ipsilateral tumor.
	Update Rationale Section
	Updated Reference Section
	Remove Appendix Section

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