Protocol

Genetic Testing for Breast Cancer Gene Expression Prognosis Assay

(20436, 20476)

Medical Benefit		**Effective Date**: 01/01/18	**Next Review Date**: 09/18
Preauthorization	Yes	**Review Dates**: 03/08, 03/09, 01/10, 01/11, 01/12, 01/13, 01/14, 11/14, 11/15, 09/16, 03/17, 09/17	

Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

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), Endopredict, Breast Cancer Index, MammaPrint (70-gene signature), Prosigna	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With early-stage node-positive invasive breast cancer considering adjuvant chemotherapy	Interventions of interest are: • Gene expression profiling with Oncotype DX (21-gene signature), Endopredict, MammaPrint (70-gene signature), Prosigna	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • 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 early-stage node-negative invasive breast cancer recurrence-free at five years, considering extended endocrine therapy	Interventions of interest are: • Gene expression profiling with Oncotype DX (21-gene signature), EndoPredict, Breast Cancer Index or Prosigna	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With breast cancer who are undergoing assessment of HER2 status	Interventions of interest are: • Assessment of HER2 status using quantitative total HER2 protein expression and HER2 homodimer measurement	Comparators of interest are: • Assessment of HER2 status using immunohistochemistry or fluorescence in situ hybridization	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity

Description

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

Novel assays that quantitatively measure total human epidermal growth factor receptor 2 (HER2) protein expression and homodimers have been developed to improve the accuracy and consistency of HER2 testing.

Summary of Evidence

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

Early-Stage Node-Negative Invasive Breast Cancer

For the evaluation of breast cancer-related gene expression profiling tests for the management of all early-stage breast cancer populations, study populations considered had positive hormone receptor status, and negative HER2 status. Only studies presenting 10-year distant recurrence rates in node-negative women not receiving adjuvant chemotherapy were included.

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, 7%-9%; upper bound of the 95% confidence intervals, 11% to 15%). These results have been demonstrated with stronger study designs for evaluating biomarkers. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

EndoPredict

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with EndoPredict, the evidence includes three 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. Over half of patients in the studies were classified at low risk. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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 one study with outcomes in node-negative patients. Although the study showed a low risk of 10-year distant recurrence, it did not derive from high-quality data sources. A recently reported study of clinical utility only reported five year results and may not identify a group with sufficiently low risk. The evidence is insufficient to determine the effects of the technology on health outcomes.

Prosigna

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with Prosigna, the evidence includes two prospective-retrospective studies evaluating the prognostic ability of Prosigna. Both studies showed a low absolute risk of distant recur-

rence in patients with low risk scores. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Early-Stage Node-Positive Invasive Breast Cancer

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 study of clinical utility only reported five-year results and may not identify a group with sufficiently low risk. The evidence is insufficient to determine the effects of the technology on health outcomes.

Extended Endocrine Therapy

Oncotype DX (21-Gene Assay)

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

EndoPredict

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

Breast Cancer Index

For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at five years who are considering extending tamoxifen treatment who receive gene expression profiling with the Breast Cancer Index, the evidence includes two studies of archived tissue samples from previously conducted clinical trials and a retrospective cohort study. The three studies showed low distant recurrence 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 lesser benefit from extended endocrine therapy. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. Clarity about how the test would inform clinical practice is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Prosigna

For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at five years who are considering extending tamoxifen treatment who receive gene expression profiling with Prosigna, the evidence includes two studies from previously conducted clinical trials examined in three publications. The studies showed low distant recurrence rates in patients classified as low risk with the test. A reclassification result would suggest that the test may offer little improvement over clinical predictors alone. Clarity about how the test would inform clinical practice is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

HER2

The evidence for assessment of HER2 status using quantitative total HER2 protein expression and HER2 homodimer measurement in patients who have breast cancer and are undergoing assessment of HER2 status includes validation studies and retrospective analysis of association between levels and survival outcomes. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Retrospective analysis using HERmark® have shown that the assay may predict a worse response to trastuzumab in certain populations. However, findings have been inconsistent, and no clear association with clinical outcomes has been shown. Additionally, cut points for defining patient groups varied across studies. Clinical utility of the HERmark® assay has not been demonstrated, and clinical trials are needed to determine the impact on clinical outcomes of patients stratified by the HERmark® assay. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

The use of gene expression assays for deciding the risk of distant recurrence in individuals with early stage breast cancer may be considered **medically necessary** for women with breast cancer meeting all of the following characteristics:

- Unilateral tumor; AND
- hormone receptor-positive (that is estrogen-receptor [ER]-positive or progesterone receptor [PR]-positive); AND
- human epidermal growth factor receptor 2 (HER2) negative; AND
- tumor size 0.6 to one cm with moderate/poor differentiation or unfavorable features OR tumor size larger than one cm; AND
- node negative or lymph nodes with micrometastases less than two mm in size; AND
- who will be treated with adjuvant endocrine therapy, e.g., tamoxifen or aromatase inhibitors; AND
- when the test result will aid the patient in making the decision regarding chemotherapy (i.e., when chemotherapy is a therapeutic option); AND
- when ordered within six months after diagnosis.

The use of the Oncotype DX, Prosigna or Endopredict RT-PCR assays may be considered **medically necessary** if the individual meets the criteria above.

The 21 gene Oncotype DX gene expression assays for deciding the value of adjuvant therapy in individuals with intermediate risk breast cancer and with ER+, Her2-cases with one to three ipsilateral lymph nodes may be considered **medically necessary**. All other gene expression assays have not been proven to predict the value of adjuvant chemotherapy in early stage breast cancer and are considered **investigational** for this purpose. (See Policy Guidelines)

The 21-gene RT-PCR assay Oncotype DX™ should only be ordered on a tissue specimen obtained during surgical removal of the tumor and after subsequent pathology examination of the tumor has been completed and determined to meet the above criteria (i.e., the test should not be ordered on a preliminary core biopsy). The test should be ordered in the context of a physician-patient discussion regarding risk preferences and when the test result will aid the patient in making decisions regarding chemotherapy.

For patients who otherwise meet the above characteristics but who have multiple ipsilateral primary tumors, a

specimen from the tumor with the most aggressive histological characteristics should be submitted for testing. It is not necessary to conduct testing on each tumor; treatment is based on the most aggressive lesion.

All other indications for multigene breast cancer panel assays, 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 **investigational**.

The use of a subset of genes from the Oncotype DX or Prosigna RT-PCR assay for predicting recurrence risk in individuals with noninvasive ductal carcinoma in situ to inform treatment planning following excisional surgery is considered **investigational**.

The use of other gene expression assays, including but not limited to MammaPrint® 70-gene signature, Mammostrat® Breast Cancer Test, the Breast Cancer Index℠, BreastOncPx™, NexCourse® Breast IHC4 and BreastPRS™, for any indication is considered **investigational**.

The use of gene expression assays in men with breast cancer is considered **investigational**.

The use of gene expression assays to molecularly subclassify breast cancer is considered **investigational**.

The use of gene expression assays for quantitative assessment of ER, PR, and HER2 overexpression is considered **investigational**.

The use of gene expression assays in tumors that are hormone receptor positive, Her2 Negative, or less than or equal to .5 cm is **investigational**.

Policy Guidelines

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

Medicare Advantage

The above medical necessity criteria applies for Medicare Advantage members for all gene expression assays in breast tumor tissue tests when no separate Medicare Advantage criteria exists.

PROSIGNA® Breast Cancer Prognostic Gene Signature Assay is considered **medically necessary** in patients who have undergone surgery in conjunction with locoregional treatment consistent with standard of care, either as:

- A prognostic indicator for distant recurrence-free survival at 10 years in post-menopausal women with Hormone Receptor-Positive (HR+), lymph node-negative, Stage I or II breast cancer to be treated with adjuvant endocrine therapy alone, when used in conjunction with other clinicopathological factors.
- A prognostic indicator for distant recurrence-free survival at 10 years in post-menopausal women with Hormone Receptor-Positive (HR+), lymph node-positive (one to three positive nodes), Stage II breast cancer to be treated with adjuvant endocrine therapy alone, when used in conjunction with other clinicopathological factors. The device is not intended for patients with four or more positive nodes.

The Breast Cancer Index (aka BCI) (bioTheranostics) may be considered **medically necessary** for members that meet the following criteria:

- Post-menopausal female with non-relapsed, ER+ BREAST CANCER, and
- Was lymph node negative, and

- Is completing five (5) years of tamoxifen therapy, and
- Patient must be eligible for consideration of extended endocrine therapy based on published clinical trial data or practice guidelines, and
- Physician or patient is concerned about continuing anti-hormonal therapy because of documented meaningful toxicity or possible significant patient-specific side effects, and
- The test results will be discussed with the patient (including the limitations of the testing method, the risks and benefits of either continuing or stopping the therapy based on the test, and current cancer management guidelines).

Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes (Oncotype DX), utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score is considered **medically necessary** to guide therapeutic decision-making in patients with the following findings:

- estrogen-receptor positive, node-negative carcinoma of the breast
- estrogen-receptor positive micrometastases of carcinoma of the breast, and
- estrogen-receptor positive breast carcinoma with one to three positive nodes.

For Medicare Advantage the HERmark®**,** and the MammaPrint™ tests may be considered **medically necessary**.

Background

Newly Diagnosed Breast Cancer

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

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

- **The decision to pursue adjuvant chemotherapy following locoregional therapy, with or without neoadjuvant chemotherapy, based on predicted risk of recurrence, for women who are hormone receptor-positive but HER2-negative. T**he use of adjuvant chemotherapy reduces the risk of breast cancer recurrence but carries risks of systemic toxicity. The risk: benefit ratio must be balanced for each patient, with a higher likelihood of net health benefits for patients with a greater baseline predicted the risk of recurrence. Some of the individual considerations are discussed below. HER2 expression independently confers an unfavorable prognosis, but assessing the independent effects of HER2 is complicated in the presence of targeted therapy; therefore, we focus specifically on patients without HER2 expression.
- **The decision to pursue adjuvant endocrine therapy from five to 10 years for women who are hormone receptor-positive but HER2-negative and who have survived without recurrence to five years**. For patients with hormone receptor-positive tumors, the use of adjuvant endocrine therapy (tamoxifen and/or an aromatase inhibitor, with or without ovarian suppression) for five to 10 years after an initial diagnosis has support in clinical practice. The 2017 guidelines from the National Comprehensive Cancer Network (NCCN) recommend extended endocrine therapy.[2] The American Society for Clinical Oncology's (ASCO) 2014

focused update to its guidelines on adjuvant endocrine therapy for women with hormone receptor–positive breast cancer have recommended 10 years of tamoxifen for pre- or perimenopausal women, and a total of seven-eight to 10 years of endocrine therapy, following one of four regimens that include tamoxifen with or without an aromatase inhibitor for postmenopausal women.[3,4]

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

Selection of Adjuvant Chemotherapy Based on Risk of Recurrence

An important part of treatment planning for women with breast cancer involves determining which patients could benefit from adjuvant cytotoxic chemotherapy. For example, for women with early-stage invasive breast cancer (i.e., cancer extending beyond the basement membrane of the mammary ducts into adjacent tissue), adjuvant cytotoxic chemotherapy consistently provides approximately a 30% relative risk reduction in 10-year breast cancer mortality regardless of patients' baseline prognosis. However, the absolute benefit of chemotherapy depends on the underlying or baseline risk of recurrence. Women with the best prognosis have tumors that are small, early-stage, estrogen receptor–positive, and lymph node negative (Table 1 shows recurrence risk for estrogen receptor–positive cancers for patients followed in the International Breast Cancer Study Group).[1] Patients may have received no adjuvant treatment, or adjuvant tamoxifen and/or adjuvant chemotherapy. These women have an approximately 15% ten-year risk of recurrence with tamoxifen alone; approximately 85% of these patients could avoid the toxicity of adjuvant cytotoxic chemotherapy if they could be accurately identified. Conventional risk classifiers (e.g., Adjuvant! Online) estimate recurrence risk by considering criteria such as tumor size, type, grade, and histologic characteristics; hormone receptor status; and number of affected lymph nodes. Consensus guidelines for defining receptor status exist.[5] However, no single classifier is considered a criterion standard. As a result, a substantial number of patients are treated with chemotherapy who fail to benefit. Better predictors of recurrence risk could help women's decision making, some of whom may prefer to avoid chemotherapy if assured their risk is low.

Table 1. Effect of Nodal Involvement, Tumor Size, and Grade on Annual Recurrence Hazard in Estrogen Receptor-Positive Breast Cancers (Colleoni et al, 2016[1])

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

[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 five years of tamoxifen improves mortality in women with hormone receptor-positive breast cancer. A 2011 individual patient data meta-analysis by the Early Breast

Cancer Trialists' Collaborative Group, including 20 trials (total N=21,457 patients) found that five years of tamoxifen in estrogen receptor–positive disease reduced the risk of recurrences by almost 50% over 10 years on the relative scale; breast cancer mortality was decreased by 29% through 15 years.[6]

For patients with early-stage, invasive breast cancer that is hormone receptor-positive, the use of endocrine therapy (tamoxifen and/or aromatase inhibitor, with or without ovarian suppression) for five to 10 years following initial diagnosis has support in national guidelines.[2, 3, 7] However, the regimens available and the evidence to support them vary.

Randomized controlled trials published recently have shown that extended endocrine therapy decreases the risk of recurrence. The ASCO and NCCN guidelines were informed primarily by results of the ATLAS trial, which compared five and 10 years of tamoxifen[8] and the subsequent aTTom trial (reported in abstract form).[9] In both trials, in women who were hormone receptor-positive and had completed five years of tamoxifen, five years of extended tamoxifen was associated with improvements in breast cancer-specific mortality; ATLAS showed improvements in overall survival (see Table 2).

Three previously reported randomized trials of extended tamoxifen treatment had mixed findings: Tormey et al (1996; total N=194 patients),[10] the National Surgical Adjuvant Breast and Bowel Project (Fisher et al, 2001; total N=1172 patients),[11] and the Scottish Cancer Trials Breast Group (Stewart et al, 2001; total N=342 patients)[12] (see Table 2).

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

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

Study	Population	Comparators	Breast Cancer–Specific Mortality		Overall Mortality	
			Event RR (95% CI)	p	Event RR (95% CI)	p
Extended tamoxifen						
ATLAS (2013)[8]	6846 women with ER-positive, early breast cancer, after five years of tamoxifen	Continue tamoxifen to 10 years (n=3428) vs. stop tamoxifen at five years (n=3418)	0.83 (0.72 to 0.96) (331/3428 vs. 397/3418)	0.01	0.87 (0.78 to 0.97) 722 (639/3428 vs. 722/3418)	0.01
aTTom (2013)[9]	6953 women with ER-positive or untested breast cancer, after five years of tamoxifen	Continue tamoxifen to 10 years (n=3468) vs. stop tamoxifen at five years (n=3485)	**10 years** 392/3468 intervention vs. 442/3485 control **Years five-nine** 1.03 (0.84 to 1.27) **After year nine** 0.77 (0.64 to 0.92)	0.05	**10 years** 849/3468 intervention vs. 910/3485 control **Years five-nine** 1.05 (0.90 to 1.22) **After year nine** 0.86 (0.75 to 0.97)	0.1
Extended aromatase inhibitor						
ABCSG (2007)[13]	856 post-menopausal women with ER- and/or PR-positive breast cancer, after five years of tamoxifen	Anastrozole for three years (n=386) vs. no further therapy (n=466)			**five years** 10.3% anastrozole vs. 11.7% control **Event HR (95% CI)** 0.89 (0.59 to 1.34)	0.57
			Breast Cancer–Specific Survival		**Overall Survival**	
NCIC CTG MA.17 trial (2003, 2005)[14,15]	5187 post-menopausal women with ER- and/or PR-positive early breast	Continue letrozole to 10 years (n=2593) vs. stop tamoxifen at five years (n=2594)	**48 Months** 94.4% letrozole vs. 89.8% placebo **Event HR**		**48 Months** 96% letrozole vs. 94% placebo **Event HR**	

Study	Population	Comparators	Breast Cancer–Specific Mortality		Overall Mortality	
	cancer, after five years tamoxifen		0.58 (0.45 to 0.76)	< 0.001	0.76 (0.48 to 0.21) **40 Months** 95.4% letrozole vs. 95% placebo **Event HR** 0.82 (0.57 to 1.19)	0.25 0.3
NSABP (2008)[16]	1598 post-menopausal women with ER- and/or PR-positive early breast cancer, after five years of tamoxifen	Planned comparison: five years exemestane vs. five years placebo. Accrual stopped (n=1598 randomized) and crossover allowed after results of NCIC CTG available: • Exemestane: 783 randomized, 560 continued after unblinding) • Placebo: 779 randomized, 334 crossed over to exemestane after unblinding	**48 Months** ITT: 91% exemestane vs. 89% placebo	0.07		

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

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

Clinical Uses of Gene Expression for Breast Cancer

In other clinical scenarios involving breast cancer, accurate assessment of prognosis may affect the decision to offer certain treatments. Recently, several groups have identified panels of gene expression markers ("signatures") that appear to predict the baseline risk of invasive breast cancer recurrence after surgery, radiotherapy, and endocrine therapy (for hormone receptor positive tumors). Several gene expression tests commercially available in the United States are listed in Table 3. If these panels are more accurate risk predictors than current conventional classifiers, they could be used to aid decision making on adjuvant treatments without greatly affecting disease-free survival and overall survival (OS). This review focuses on gene expression profiling panels that have prognostic or predictive ability in individuals with early-stage, invasive breast cancer with known estrogen receptor and progesterone receptor and human epidermal growth factor receptor (HER2) status. The proposed clinical utility of these tests varies by the clinical context; these specific indications are discussed in this review:

- 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 (one – three 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 chemo-therapy.

- Prognosis and/or prediction of treatment response in patients with DCIS 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 five years postdiagnosis, for the purpose of determining whether patients will continue adjuvant hormonal therapy.

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

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

Test	Manufacturer	Description
Oncotype DX®	Genomic Health (Redwood City, CA)	21-gene RT-PCR
EndoPredict®	Sividon Diagnostics (acquired by Myriad [Salt Lake City, UT] in 2016)	12-gene real-time RT-PCR
Breast Cancer Index Prognostic℠	Biotheranostics (San Diego, CA)	Combines MGI and the HOXB13:IL17BR Index measured using RT-PCR
MammaPrint®	Agendia (Amsterdam, The Netherlands)	70-gene DNA microarray
Prosigna®	NanoString Technologies (Seattle, WA)	Gene expression protein signature Predictive signature based on nCounter® digital analysis system based on PAM50 breast cancer intrinsic subtype classifier

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

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

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

Decision Framework for Evaluating Breast Cancer Biomarkers

Simon et al Framework

Many studies have investigated individual biomarkers or combinations of biomarkers associated with breast cancer outcomes. Determining which studies constitute sufficient evidence that the test or biomarker is likely to be clinically useful depends on attributes of the test such as its performance and the quality of the study generating the results. Simon et al (2009) have described a framework to evaluate prognostic biomarker evidence.[17] Study designs such as prospective clinical trials or previously conducted clinical trials with archived tumor samples constitute stronger evidence than studies with less planned and systematic patient recruitment and data collection. Randomized trials allow determination of treatment-biomarker interactions that may be clinically important. In some clinical scenarios, demonstration of a treatment-biomarker interaction is not critical, because the decision to withhold chemotherapy in a low-risk group (to avoid chemotherapy-related morbidity) does not require the presence of a biomarker-treatment interaction. The study must generate an absolute estimate of outcomes in the patient group of interest that would result in a change in management (e.g.,

withholding of chemotherapy), and the study must have sufficient precision (narrow confidence intervals). Results of the same test across studies should show the consistency of results and more than one study demonstrating the desired result should be available. Simon has proposed that at least two Simon category B studies showing results consistent with clinical utility are necessary to demonstrate adequate evidence of a biomarker.[17]

Breast Cancer-Specific Outcomes

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

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

How these estimates correspond to the distant recurrence rates reported in prognostic studies is imprecise, but Henderson (2015) has suggested that below a recurrence threshold of 10% many patients will not elect adjuvant chemotherapy owing to the small absolute benefit.[23] He also noted that a majority of those patients are older with small node-negative tumors. That interpretation is consistent with a recent study of 81 women by Hamelinck et al (2016) who found that 78% of women ages 40 to 49 years, 88% ages 50 to 59, 59% ages 60 to 69, and 40% age 70 or older would accept adjuvant chemotherapy for a 0% to 10% absolute decrease in recurrence risk (see Table 4).[24] There was a wide range of minimally required absolute benefits, with the majority accepting chemotherapy for an absolute benefit of 1% to 5%. At a given age range, fewer women expressed a willingness to accept adjuvant endocrine therapy than chemotherapy for a given mortality benefit.

Table 4. Patient Preferences for Undergoing Adjuvant Therapy for < 10% Reduction in Recurrence Risk[24]

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

HER2

The human epidermal growth factor receptor (HER) family of receptor tyrosine kinases (EGFR/HER1, ErbB2/HER2, ErbB3/HER3, ErbB4/HER4) plays a major role in the pathogenesis of many solid tumors. In approximately 25% to 30% of breast cancers, overexpression of HER2 has been linked to shorter disease-free (DFS) and overall

survival (OS), lack of responsiveness to tamoxifen antiestrogen therapy, and altered responsiveness to a variety of cytotoxic chemotherapy regimens.

Trastuzumab, a monoclonal antibody directed at the extracellular domain of HER2 has offered significant DFS and OS advantages in the metastatic and adjuvant settings in HER2-overexpressing patients, although not all patients respond. Fewer than 50% of patients with metastatic HER2-positive breast cancer show initial benefit from trastuzumab treatment, and many of those eventually develop resistance.[1]

Current methodologies for the selection of HER2-positive patients include immunohistochemistry (IHC) to detect HER2 protein overexpression, and fluorescence in situ hybridization (FISH) to detect HER2 gene amplification. However, controversy still exists regarding the accuracy, reliability, and interobserver variability of these assay methods. IHC provides a semiquantitative measure of protein levels (scored as 0, 1+, 2+, 3+) and the interpretation may be subjective. FISH is a quantitative measurement of gene amplification, in which the HER2 gene copy number is counted. However, FISH, which is considered to be more quantitative analytically, is not always representative of protein expression, and multiple studies have failed to demonstrate a relationship between HER2 gene copy number and response to trastuzumab. Whereas patients who overexpress HER2 protein (IHC) or show evidence of HER2 gene amplification (FISH) have been shown to experience better outcomes on trastuzumab than those scored negative by those assays, differences in the degree of expression or amplification by these methods have generally not been shown to discriminate between groups with different outcomes. IHC and FISH testing may be affected by interlaboratory variability, and neither test provides quantitative data that reflect the activation state of signaling pathways in tumors, which may limit their utility in patient selection.[2] Most laboratories in North America and Europe use IHC to determine HER2 protein status, with equivocal category results (2+) confirmed by FISH (or more recently by chromogenic in situ hybridization [CISH]).

Normally, HER2 activates signaling pathways by dimerizing with ligand-bound EGFR-family members such as HER1 and HER3. A HER2 ligand has not been identified, but overexpressed HER2 is constitutively active. When HER2 is pathologically overexpressed, the receptor may homodimerize and activate signaling cascades in the absence of the normal regulatory control imposed by the requirement for ligand binding of its heterodimerization partners.

A novel assay (HERmark® Breast Cancer Assay; Monogram Biosciences, South San Francisco, CA) was developed to quantify total HER2 protein expression (H2T) and HER2 homodimers (H2D) in formalinfixed, paraffin-embedded tissue samples.

Regulatory Status

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

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

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

Product Code: NYI.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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