Protocol

Genetic Testing for Breast Cancer Gene Expression Prognosis Assay

(20436, 20476)

Medical Benefit		Effective Date: 02/01/20	Next Review Date: 09/20
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, 09/18, 11/19	

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, MammaPrint (70-gene signature) 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: • Quantitative total HER2 protein expression and HER2 homodimer measurement	Comparators of interest are: • Assessment of HER2 status using immunohisto-chemistry or fluorescence in situ hybridization	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity

DESCRIPTION

Laboratory tests have been developed to detect the expression, via messenger RNA, of different genes in breast tumor tissue and combine the results into a prediction of distant recurrence risk for women with early-stage breast cancer. Test results may help providers and patients decide whether to include adjuvant chemotherapy in the postsurgical management of breast cancer, to alter treatment in patients with ductal carcinoma in situ (DCIS), or to recommend extended endocrine therapy in patients who are recurrence-free at five years. This report summarizes the evidence for five tests, which are organized by indication: Oncotype DX, EndoPredict, Breast Cancer Index, MammaPrint, and Prosigna.

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 human epidermal growth factor receptor 2 (HER2) status. Studies retrospectively collecting tumor samples from prospective trials that provide at least five-year distant recurrence rates or at least five-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 ten years, 3%-7%; upper bound of the 95% confidence interval [CI], 6% to 10%). These results have been demonstrated with stronger study designs for evaluating biomarkers. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

EndoPredict

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with EndoPredict, the evidence includes three prospective-retrospective studies and observational studies. The studies revealed that a low score was associated with a low absolute risk of ten-year distant recurrence (average risk at ten years for the two larger studies, 3%-6%; upper bound of the 95% CI, 6% to 9%). Over half of the patients in these studies were classified as low-risk. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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 ten-year distant metastases-free survival for the low-risk group treated with tamoxifen (93%; 95% CI, 88% to 96%), but not as high survival for the low-risk group not treated with tamoxifen (83%, 95% CI, 76% to 88%). The randomized controlled trial Microarray in Node-Negative and one to three Positive Lymph Node Disease May Avoid Chemotherapy showed five-year distance recurrence rates below the 10%

threshold among patients identified as low-risk. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Prosigna

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with Prosigna, the evidence includes two prospective-retrospective studies evaluating the prognostic ability of Prosigna. Both studies showed a low absolute risk of distant recurrence in patients with low risk scores (average risk at 10 years, 3%-5%; upper bound for the study providing CI, 6%). The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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 two prospective-retrospective studies and a registry-based observational study. The findings from the two prospective-retrospective studies showed that a low-risk Breast Cancer Index score is associated with low ten-year distant recurrence rates (average risk at ten years, 5%-7%; upper bound of the 95% CI, 8% to 10%). The findings from the registry-based observational study also showed low ten-year distant recurrence rates. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

EARLY-STAGE NODE-POSITIVE (1 TO 3 NODES) INVASIVE BREAST CANCER

For decisions on the management of early-stage node-positive disease, Oncotype DX, Endopredict, Mammaprint, and Prosigna were evaluated. Only studies presenting a minimum of five-year distant recurrence rates or five-year survival rates were included in this part of the evidence review.

MammaPrint (70-gene signature)

For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with MammaPrint (70-gene signature), the evidence includes a clinical utility study and an observational study. The study of clinical utility reported five-year results and may not identify a group with sufficiently low-risk. The observational study reported the low-risk group experienced a low rate of ten-year distant recurrence. The evidence is sufficient to determine the effects of the technology on health outcomes.

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

EndoPredict

For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with EndoPredict, the evidence includes two prospective-

retrospective analyses. In one study, the ten-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 ten-year distant recurrence rate in low-risk EndoPredict score patients was estimated to be 5% but the upper bound of the 95% CI was close to 20%. To establish that the test has the potential for clinical utility, it should be able to identify a low-risk group with a recurrence risk that falls within a range that is clinically meaningful for decision-making about avoiding adjuvant chemotherapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

Prosigna

For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemo-therapy who receive gene expression profiling with the Prosigna risk of recurrence (ROR) score, the evidence includes a single prospective-retrospective study. The ten-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 ten-year distant recurrence in node-positive patients classified as ROR score low-risk was about 13%, which approaches the range judged clinically informative in node-negative patients. The predicted recurrence rates require replication. To establish that the test has the potential for clinical utility, it should be able to identify a low-risk group with a recurrence risk that falls within a range that is clinically meaningful for decision-making about avoiding adjuvant chemotherapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

DUCTAL CARCINOMA IN SITU

The Oncotype DX Breast DCIS Score is the only assay investigated for patients with DCIS.

Oncotype DX Breast DCIS Score

For individuals who have DCIS considering radiotherapy who receive gene expression profiling with the Onco-type DX Breast DCIS Score, the evidence includes a prospective-retrospective study and a retrospective cohort study. Although the studies have shown that the test stratifies patients into high- and low-risk groups, they have not yet demonstrated with sufficient precision that the risk of disease recurrence in patients identified with a Breast DCIS Score is low enough to consider changing the management of DCIS. The evidence is insufficient to determine the effects of the technology on health outcomes.

EXTENDED ENDOCRINE THERAPY

For this indication, Oncotype DX, EndoPredict, Breast Cancer Index, MammaPrint, and Prosigna were evaluated. Studies retrospectively collecting tumor samples from prospective trials that provided ten-year distant recur-rence rates or ten-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 five years who are considering extending endocrine treatment who receive gene expression profiling with Onco-type DX (21-gene assay), the evidence includes two studies using data from the same previously conducted clini-cal 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 predic-tion tool was not reported. The evidence is insufficient to determine the effects of the technology on health outcomes.

EndoPredict

For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at five years who are considering extending endocrine treatment who receive gene expression profiling with Endo-Predict, the evidence includes two analyses of archived tissue samples from two previously conducted clinical

trials. The studies showed low distant recurrence rates in patients classified as low-risk with EndoPredict. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. Additional prospective trials or retrospective-prospective studies of archived samples reporting on the association between risk score and survival are needed to confirm results from the single study. More importantly, clarity is needed about how the test would inform clinical practice. The evidence is insufficient to determine the effects of the technology on health outcomes.

MammaPrint (70-Gene Signature)

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 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 ten- and 20-year breast cancer-specific survival rates. Additional studies are needed to confirm the results of this single study. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. Clarity about how the test would inform clinical practice is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Prosigna

For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at five 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 three publications. The studies showed low distant recurrence rates in patients classified as low-risk with the test. A reclassification result suggested that the test may offer little improvement over clinical predictors alone. Clarity about how the test would inform clinical practice is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 three analyses of archived tissue samples from two previously conducted clinical trials and a retrospective cohort study. The analyses showed low distant recurrence rates and high distant recurrence-free survival rates in patients classified as low-risk with the test. Two studies suggested that, in addition to having a more favorable prognosis, low-risk patients may receive less benefit from extended endocrine therapy. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. Clarity about how the test would inform clinical practice is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

HER2

For individuals who have breast cancer and are undergoing assessment of HER2 status who receive quantitative total HER2 protein expression and HER2 homodimer measurement, the evidence includes validation studies and retrospective analysis of the 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

The use of gene expression assays for deciding the value of adjuvant therapy in individuals with early-stage node-negative breast cancer may be considered **medically necessary** for women 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 greater than 0.5 cm with moderate/poor differentiation or unfavorable features; 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 chemo-therapy is a therapeutic option); AND

- when ordered within six months after diagnosis.

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

For individuals who have early-stage node-positive breast cancer, who are at a high clinical risk of recurrence and who meet all other indications as above, but who have one to three positive lymph nodes (in place of "node negative or lymph nodes with micrometastases less than two mm in size"), the use of MammaPrint to inform decisions on adjuvant systemic chemotherapy may be considered **medically necessary**.

The use of Oncotype DX, Prosigna or Endopredict RT-PCR are considered **investigational** for individuals with early-stage node-positive breast cancer as described in the above statement.

The use of MammaPrint is considered **investigational** in individuals who have a low clinical risk for recurrence (per MINDACT trial categorization.)

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 deter-mined 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 inva-sive 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 (i.e., Oncotype DX® Breast DCIS Score) to inform treatment planning following excisional surgery is considered **investigational**.

The use of other gene expression assays, including but not limited to, Mammostrat® Breast Cancer Test, Breast OncPx™, 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**.

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.

*Women meeting these criteria whose MammaPrint score is low may be treated with hormone therapy alone, as it is unlikely that chemotherapy will provide substantial additional benefits (per MINDACT trial categorization).

GENETIC COUNSELING

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

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

- Is 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, <u>and</u>

- Physician or patient is concerned about continuing anti-hormonal therapy because of documented meaningful toxicity or possible significant patient-specific side effects, <u>and</u>

- 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 are considered **medically necessary**.

For Medicare Advantage the Oncotype DX® DCIS assay (Genomic Health, Inc., Redwood City, CA) is considered **medically necessary** for women diagnosed with DCIS who are planning on having breast conserving surgery and considering adjuvant radiation therapy only when the following clinical conditions are met:

- Pathology (excisional or core biopsy) reveals ductal carcinoma in situ of the BREAST (no pathological evidence of invasive disease), and

- FFPE specimen with at least 0.5 mm of DCIS length, and

- Patient is a candidate for and is considering breast conserving surgery alone as well as breast conserving surgery combined with adjuvant radiation therapy, and

- Test result will be used to determine treatment choice between surgery alone vs. surgery with radiation therapy, and

- Patient has not received and is not planning on receiving a mastectomy.

For Medicare Advantage, the EndoPredict® breast cancer gene expression test (Myriad Genetic Laboratories Inc., Salt Lake City, UT) is considered **medically necessary** for the management of post-menopausal women diagnosed with early-stage (TNM stage T1-3, N0-1) estrogen-receptor (ER) positive, HER2-negative breast cancer, who are either lymph node-negative or who have 1-3 positive nodes, and for whom treatment with adjuvant endocrine therapy (e.g., tamoxifen or aromatase inhibitors) is being considered.

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:

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

2. The decision to pursue adjuvant endocrine therapy from five to ten years for women who are hormone receptor-positive but HER2-negative and who have survived without recurrence for 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 ten years after an initial diagnosis has support in clinical practice. The guidelines from the National Comprehensive Cancer Network (v.1.2019) do not recommend extended endocrine therapy, but state that aromatase inhibitors or tamoxifen may be considered following five years of endocrine therapy for certain women, depending on menopausal status and prior treatment history. The guidelines also note that the optimal duration of aromatase inhibitors is uncertain.[2] The American Society for Clinical Oncology (2018) updated its guidelines from 2014[3,4] on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer.[5] The update included a qualifying statement that none of the studies used to develop the recommendations showed improvements in overall survival (OS) with extended therapy, and that the recommendations are based on benefits that include prevention of distant recurrence and prevention of second breast cancers. Therefore, the decision to receive extended therapy should involve the weighing of recurrence risk against potential therapy risks and side effects. Recommendations based on nodal status are as follows:

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

   - Women with node-positive breast cancer should be offered extended AI therapy for up to a total of ten years of adjuvant endocrine therapy.

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

SELECTION OF ADJUVANT CHEMOTHERAPY BASED ON RISK OF RECURRENCE

An important part of treatment planning for women with breast cancer involves determining which patients could benefit from adjuvant cytotoxic chemotherapy. For example, for women with early-stage invasive breast cancer (i.e., cancer extending beyond the basement membrane of the mammary ducts into adjacent tissue), adjuvant cytotoxic chemotherapy consistently provides approximately a 30% relative risk reduction in ten 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, which means that approximately 85% of these patients could avoid the toxicity of adjuvant cytotoxic chemotherapy if they could be accurately identified. Conventional risk classifiers (e.g., Adjuvant! Online) estimate recurrence risk by considering criteria such as tumor size, type, grade, and histologic characteristics; hormone receptor status; and the number of affected lymph nodes. Consensus guidelines for defining receptor status exist[6]; however, no single classifier is considered a criterion standard. As a result, a substantial number of patients are treated with chemotherapy who fail to benefit. Better predictors of recurrence risk could help women's decision-making, some of whom may prefer to avoid chemotherapy if assured their risk is low.

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

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

Adapted from Colleoni et al (2016).[1]

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

SELECTION OF EXTENDED ENDOCRINE THERAPY

Randomized controlled trials have established that 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=21457 patients), found that five 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.[6]

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

These randomized controlled trials have shown that extended endocrine therapy decreases the risk of recurrence. The Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial, which compared five and ten years of tamoxifen,[10] and the subsequent Long-term Effects of Continuing Adjuvant Tamoxifen to 10 Years versus stopping at five Years (aTTom) trial (reported in abstract form)[11] included women who were hormone receptor-positive who had completed five years of tamoxifen. Five years of extended tamoxifen was associated with improvements in breast cancer-specific mortality in both ATLAS and aTTom; however, only ATLAS showed improvements in OS (see Table 2).

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

Guidelines for Extended Endocrine Therapy

For patients with early-stage, invasive breast cancer that is hormone receptor-positive, the use of endocrine therapy (tamoxifen and/or an aromatase inhibitor, with or without ovarian suppression) for the initial five years following initial diagnosis has support in national guidelines.[2,3,18] Support for extended endocrine therapy beyond the initial five years is inconsistent across various guidelines.

The latest guidelines from the American Society for Clinical Oncology (2014) discuss extended endocrine therapy for breast cancer have recommended an additional five years of tamoxifen for premenopausal women and five years of aromatase inhibitors for postmenopausal women.[4] National Comprehensive Cancer Network guidelines (v.1.2019) do not recommend extended endocrine therapy, but state that aromatase inhibitors or tamoxifen may be considered following five years of endocrine therapy. The guidelines also note that the optimal duration of aromatase inhibitors is uncertain.[2]

Adverse Events From Extended Endocrine Therapy

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

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

Study	Population	Comparators	Breast Cancer–Specific Mortality		Overall Mortality	
			Event RR (95% CI)	p	Event RR (95% CI)	p
Extended tamoxifen						
ATLAS (2013)[10]	6846 women with ER-positive, early breast cancer, after 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)[11]	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)[12]	856 post-menopausal women with ER-	Anastrozole for three years (n=386) vs. no further therapy			**five years** 10.3% anastrozole vs. 11.7% control	0.57

Study	Population	Comparators	Breast Cancer–Specific Mortality		Overall Mortality	
	and/or PR-positive breast cancer, after five years of tamoxifen	(n=466)			**Event HR (95% CI)** 0.89 (0.59 to 1.34)	
			Breast Cancer– Specific Survival		**Overall Survival**	
IDEAL (2018)[17]	1824 post-menopausal women with ER- and/or PR-positive early breast cancer, after five years of endocrine therapy	Letrozole for 2.5 years (n=909) or five years (n=915)	**Median 6.6 Years** 2.5 years: 82.0% five years: 83.3%	0.5	**Median 6.6 Years** 2.5 years: 89.4% five years: 88.6%	NS
DATA (2017)[16]	1912 post-menopausal women with ER- and/or PR-positive early breast cancer, after two-three years of tamoxifen	Anastrozole for three years (n=955) or six years (n=957)	**Five Years** Three years: 79.4% Six years: 83.1%	0.06	**Five Years** Three years: 90.4% Six years: 90.8%	0.6
NSABP (2008)[15]	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		
NCIC CTG MA.17 trial (2003, 2005)[13,14]	5187 post-menopausal women with ER- and/or PR-positive early breast cancer, after five years of tamoxifen	Continue letrozole to ten years (n=2593) vs. stop tamoxifen at five years(n=2594)	**48 Months** 94.4% letrozole vs. 89.8% placebo Event HR 0.58 (0.45 to 0.76)	<0.001	**48 Months** 96% letrozole vs. 94% placebo **Event HR** 0.76 (0.48 to 0.21) **40 Months** 95.4% letrozole vs. 95% placebo **Event HR** 0.82 (0.57 to 1.19)	0.25 0.3

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

In addition to the trials published in full-length form, two trials were presented in early 2017 evaluating extended endocrine therapy in postmenopausal women (NSABP-42 [NCT00382070]: ten years vs. five years of letrozole; and IDEAL [NTR3077] ten years vs. 7.5 years of letrozole) did not meet their primary endpoints.

CLINICAL USES OF GENE EXPRESSION SIGNATURES FOR BREAST CANCER

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

1. Prognosis and/or prediction of treatment response in patients with node-negative, early-stage, hormone receptor-positive, HER2-negative invasive breast cancer who will receive adjuvant hormonal therapy for the purpose of determining whether patients can avoid adjuvant cytotoxic chemotherapy.

2. Prognosis and/or prediction of treatment response in patients with node-positive (one to 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 chemotherapy.

3. Prognosis and/or prediction of treatment response in patients with DCIS for the purpose of determining whether patients can avoid radiotherapy.

4. Prognosis and/or prediction of treatment response in patients with node-negative, early-stage, hormone receptor-positive, HER2-negative invasive breast cancer, receiving adjuvant hormonal therapy, who have survived without progression to five years post diagnosis, 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 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 (Redwood City, CA)	21-gene RT-PCR; identifies three 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

Test	Manufacturer	Description
Breast Cancer Index Prognostic[SM]	Biotheranostics	Combines MGI and the HOXB13: IL17BR Index measured using RT-PCR; identifies 2 groups as low or high risk for distant recurrence
MammaPrint®	Agendia	70-gene DNA microarray; identifies two groups as low or high risk for distant recurrence
Prosigna®	NanoString Technologies	Gene expression profile is assessed by the nCounter digital platform system to determine similarity with prototypic profiles of PAM50 genes for breast cancer; identifies 3 categorical ROR groups (ROR-low, ROR-intermediate, ROR-high)

MGI: Molecular Grade Index; PAM50: prediction analysis of microarray 50-gene set; 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 (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 the response to chemotherapy.

DECISION FRAMEWORK FOR EVALUATING BREAST CANCER BIOMARKERS

Simon et al Framework

Many studies have investigated individual biomarkers or combinations of biomarkers associated with breast cancer outcomes. Determining which studies constitute sufficient evidence that the test or biomarker is likely to be clinically useful depends on attributes of the test such as its performance and the quality of the study generating the results. Simon et al (2009) have described a framework to evaluate prognostic biomarker evidence.[22] Study designs, such as prospective clinical trials or previously conducted clinical trials with archived tumor samples, constitute stronger evidence than studies with less planned and systematic patient recruitment and data collection. Randomized trials allow determination of treatment-biomarker interactions that may be clinically important. In some clinical scenarios, demonstration of a treatment-biomarker interaction is not critical, because the decision to withhold chemotherapy in a low-risk group (to avoid chemotherapy-related morbidity) does not require the presence of a biomarker-treatment interaction. The study must generate an absolute estimate of outcomes in the patient group of interest that would result in a change in management (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 et al (2009) have proposed that at least two Simon et al (2009) category B studies showing results consistent with clinical utility are necessary to demonstrate adequate evidence of a biomarker.[22] Simon et al (2009) also proposed that while "further confirmation in a separate trial of the results gained from a category A prospective trial is always welcome, compelling results from such a trial would be considered definitive and no other validating trial would be required."[22]

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, ten-year distant recurrence has been the outcome of interest for assessing prognostic tests used to select women with early-stage breast cancer who can avoid treatment with adjuvant chemotherapy.[23] The Early Breast Cancer Trialists' Collaborative Group (2012) conducted a patient data meta-analysis of 123 trials (N>100000 women) that compared various chemotherapy regimens with no chemotherapy for early-stage breast cancer.[24] The pooled results showed that women receiving chemotherapy experienced significantly lower rates of distant recurrence compared with women not receiving chemotherapy for up to five years; however, during the five to ten year follow-up period, recurrence rates were similar between the two groups. This would suggest that any benefit of chemotherapy can be observed with five years of follow-up. As a result, BCBSA has revised the requirement for the duration of follow-up from ten to five years when assessing prognosis in women considering adjuvant chemotherapy.

Decisions to undergo or forgo adjuvant therapy (chemotherapy or endocrine) depend on how a woman values the potential benefit of lower recurrence risk relative to the harms of treatment. The balance of benefits and harms determines the thresholds that inform decisions.[25,26] Most women will accept substantial adverse events for even modest benefit. For example, Simes et al (2001) interviewed 104 Australian women with breast cancer treated with cytotoxic chemotherapy and elicited preferences to undergo chemotherapy according to probable gain in survival.[27] With an expected survival of five years without chemotherapy, 73% said they would accept chemotherapy for 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.[28] About half felt a single day would justify adjuvant chemotherapy. A major difference between the two studies was that the chemotherapy regimen in the Duric et al (2005) study was less toxic. Thewes et al (2005) adopted the same approach for adjuvant endocrine therapy preferences in 102 premenopausal women with early-stage breast cancers.[29] Among women having a baseline life expectancy of 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 et al (2005).

How these estimates correspond to the distant recurrence rates reported in prognostic studies is imprecise, but Henderson (2015) has suggested that below a recurrence threshold of 10% many patients will not elect adjuvant chemotherapy owing to the small absolute benefit.[30] He also noted that a majority of those patients are older with small node-negative tumors. That interpretation is consistent with a recent study of 81 women by Hamelinck et al (2016) who found that 78% of women ages 40 to 49 years, 88% ages 50 to 59, 59% ages 60 to 69, and 40% age 70 or older would accept adjuvant chemotherapy for a 0% to 10% absolute decrease in recurrence risk (see Table 4).[31] There 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, 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

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

HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2

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 and overall survival, 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 shorter disease-free and overall survival 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.[1,2,3]

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 inter-observer variability of these assay methods. IHC provides a semi-quantitative 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 relation 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 inter-laboratory 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.[4] 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).

Typically, HER2 activates signaling pathways by dimerizing with ligand-bound epidermal growth factor receptor 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) was developed to quantify total HER2 protein expression and HER2 homodimers in formalin-fixed, 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 must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Oncotype DX®, HERmark® Breast Cancer Assay (Monogram Biosciences) 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[SM] (Biotheranostics) and EndoPredict® (distributed by Myriad) are not FDA-approved.

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

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and post payment 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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