FEP 2.04.36 Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients With Breast Cancer

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Related Policies: None

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

Description

Laboratory tests have been developed that detect the expression, via messenger RNA, of many different genes in breast tumor tissue and combine the results into a prediction of distant recurrence risk for women with early-stage breast cancer. Test results may help providers and patients decide whether to include adjuvant chemotherapy in the postsurgical management of breast cancer, to alter treatment in patients with ductal carcinoma in situ (DCIS), or to recommend extended endocrine therapy in patients who are recurrence-free at 5 years. This report summarizes the evidence of 5 tests, which are organized by indication: Oncotype DX, EndoPredict, Breast Cancer Index, MammaPrint, and Prosigna. For all tests and all indications, relevant outcomes include disease-specific survival and changes in disease status.

FDA 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 the Clinical Laboratory Improvement Amendments. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

In February 2007, MammaPrint® (Agendia) was cleared for marketing by the FDA through the 510(k) process for the prediction of breast cancer metastasis. In January 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 September 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®.

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

POLICY STATEMENT

The use of the 21-gene reverse transcriptase polymerase chain reaction (RT-PCR) assay (ie, Oncotype DX®) to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy may be

considered **medically necessary** in women with primary, invasive breast cancer meeting all of the following characteristics:

- unilateral tumor;
- hormone receptor–positive (ie, estrogen receptor–positive or progesterone receptor–positive);
- human epidermal growth factor receptor 2–negative;
- tumor size 0.6 to 1 cm with moderate or poor differentiation or unfavorable features OR tumor size larger than 1 cm;
- node-negative (lymph nodes with micrometastases [<2 mm in size] are considered node-negative for this policy statement);
- who will be treated with adjuvant endocrine therapy (eg, tamoxifen, aromatase inhibitors);
- when the test result aids the patient in deciding on chemotherapy (ie, when chemotherapy is a therapeutic option); AND
- when ordered within 6 months after diagnosis, because the value of the test for making decisions regarding delayed chemotherapy is unknown.

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

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

Use of EndoPredict, the Breast Cancer Index, and Prosigna to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy may be considered **medically necessary** in women with primary, invasive breast cancer with the same characteristics as considered medically necessary for Oncotype DX.

All other indications for the 21-gene RT-PCR assay (ie, Oncotype DX), EndoPredict, the Breast Cancer Index, and Prosigna, including determination of recurrence risk in invasive breast cancer patients with positive lymph nodes, patients with bilateral disease, or to consider the length of treatment with tamoxifen, are considered **investigational**.

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

Use of 70-gene signature (MammaPrint) for any indication is considered **investigational**.

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

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

POLICY GUIDELINES

GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may

reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Unfavorable features that may prompt testing in tumors from 0.6 to 1 cm in size include the following: angiolymphatic invasion, high histologic grade, or high nuclear grade.

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

Current American Society of Clinical Oncology and College of American Pathologists joint guidelines on *HER2* testing in breast cancer (Wolff et al, 2013) have defined positive, negative, and equivocal *HER2* test results.

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

RATIONALE

Summary of Evidence

Early-Stage Node-Negative Invasive Breast Cancer

For the evaluation of breast cancer–related gene expression profiling tests for the management of all early-stage breast cancer populations, study populations considered had positive hormone receptor status, and negative *HER2* status. Studies retrospectively collecting tumor samples from prospective trials that provide 10-year distant recurrence rates or 10-year survival rates in node-negative women not receiving adjuvant chemotherapy were included in this part of the evidence review.

Oncotype DX (21-Gene Assay)

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with Oncotype DX (21-gene assay), the evidence includes multiple prospective clinical trials and prospective-retrospective studies. Patients classified as low risk with Oncotype DX have a low risk of recurrence in which avoidance of adjuvant chemotherapy is reasonable (average risk at 10 years, 3%-7%; upper bound of the 95% CI, 6% to 10%). These results have been demonstrated with stronger study designs for evaluating biomarkers. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

EndoPredict

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with EndoPredict, the evidence includes 3 prospective-retrospective studies and observational studies. The studies revealed that a low score was associated with a low absolute risk of 10-year distant recurrence (average risk at 10 years for the 2 larger studies, 3%-6%; upper bound of the 95% CI, 6% to 9%). Over half of patients in these studies were classified at low risk. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Breast Cancer Index

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

MammaPrint (70-Gene Signature)

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with MammaPrint (70-gene signature), the evidence includes a prospective-retrospective study and a study using a cancer registry cohort. The prospective-retrospective study reported high 10-year distant metastases-free survival for the low-risk group treated with tamoxifen (93%; 95% CI, 88% to 96%), but not as high survival for the low-risk group not treated with tamoxifen (83%, 95% CI, 76% to 88%). Although the registry study showed a low risk of 10-year distant recurrence, the source is not considered high-quality. A recently reported study of clinical utility only reported 5-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 2 prospective-retrospective studies evaluating the prognostic ability of Prosigna. Both studies showed a low absolute risk of distant recurrence in patients with low-risk scores (average risk at 10 years, 3%-5%; upper bound 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.

Early-Stage Node-Positive Invasive Breast Cancer

For decisions on management of early-stage node-positive disease, Oncotype DX, EndoPredict, MammaPrint, and Prosigna were evaluated. Only studies presenting 10-year distant recurrence rates or 10-year survival rates were included in this part of the evidence review.

Oncotype DX (21-Gene Assay)

For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with Oncotype DX (21-gene assay), the evidence includes 2 prospective-retrospective studies and a prospective study. The prospective-retrospective studies showed that Oncotype DX stratifies node-positive patients into high and low risk for distant recurrence-free survival. However, only one of the studies reported CIs for estimates and those are very wide. The prospective study included patients with node-negative and node-positive breast cancer. The authors reported that subgroup analyses of patients with node-positive breast cancer who were classified as low risk experienced higher rates of survival than patients classified as high risk, though no rates were provided. There is a wide range of survival improvements over which individual patients would elect or refuse adjuvant chemotherapy, but accurate risk estimates are needed to inform patient decisions. The evidence is insufficient to determine the effects of the technology on health outcomes.

EndoPredict

For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with EndoPredict, the evidence includes 2 prospective-retrospective analyses. In a study, the 10-year distant recurrence rate in low-risk EPclin score patients was estimated to be 5% (95% CI, 1% to 9%). In the other study, 10-year distant recurrence rate

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

MammaPrint (70-Gene Signature)

For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with MammaPrint (70-gene signature), the evidence includes a clinical utility study and an observational study. The study of clinical utility only reported 5-year results and may not identify a group with sufficiently low risk. The observational study reported that the low-risk group experienced a low rate of 10-year distant recurrence; however, the standard error around the rate did not meet the threshold benefit of less than 10%. The evidence is insufficient to determine the effects of the technology on health outcomes.

Prosigna

For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with the Prosigna ROR score, the evidence includes a single prospective-retrospective study. The 10-year distant recurrence rate in low-risk Prosigna ROR patients with a single positive node is roughly twofold the rate in low-risk ROR score node-negative patients. However, in the single available study, the upper bound of the 95% CI for 10-year distant recurrence in node-positive patients classified as ROR score low-risk was about 13%, which approaches the range judged clinically informative in node-negative patients. The predicted recurrence rates require replication. To establish that the test has potential for clinical utility, it should be able to identify a low-risk group with a recurrence risk that falls within a range that is clinically meaningful for decision-making about avoiding adjuvant chemotherapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ductal Carcinoma In Situ

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

Oncotype DX Breast DCIS Score

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

Extended Endocrine Therapy

For this indication, Oncotype DX, EndoPredict, Breast Cancer Index, MammaPrint, and Prosigna were evaluated. Studies retrospectively collecting tumor samples from prospective trials that provided 10-year distant recurrence rates or 10-year survival rates were included in this part of the evidence review. Studies comparing genetic assays with clinical risk prediction tools were also included.

Oncotype DX (21-Gene Assay)

For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending endocrine treatment who receive gene expression profiling with Oncotype DX (21-gene assay), the evidence includes 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 CIs were presented. The ability of the test to reclassify patients assessed with a clinical prediction

tool was not reported. The evidence is insufficient to determine the effects of the technology on health outcomes.

EndoPredict

For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending endocrine treatment who receive gene expression profiling with EndoPredict, the evidence includes a study of archived tissue samples from a previously conducted clinical trial. The study 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 for confirmation of results from the single study. More importantly, clarity is needed about how the test would inform clinical practice. The evidence is insufficient to determine the effects of the technology on health outcomes.

Breast Cancer Index

For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending tamoxifen treatment who receive gene expression profiling with the Breast Cancer Index, the evidence includes 3 analyses of archived tissue samples from two previously conducted clinical trials and a retrospective cohort study. The analyses showed low distant recurrence rates and high distant recurrence-free survival rates in patients classified as low risk with the test. Two studies suggested that, in addition to having a more favorable prognosis, low-risk patients may receive less benefit from extended endocrine therapy. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. Clarity about how the test would inform clinical practice is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

MammaPrint (70-Gene Signature)

For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending tamoxifen treatment who receive gene expression profiling with MammaPrint (70-gene signature), the evidence includes a retrospective-prospective study. Analyses on patients classified as ultralow risk (a subgroup of the low-risk group) showed that this ultralow-risk group experienced high 10- and 20-year breast cancer–specific survival rates. Additional studies are needed to confirm the results of this single study. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. Clarity about how the test would inform clinical practice is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Prosigna

For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending tamoxifen treatment who receive gene expression profiling with Prosigna, the evidence includes 2 studies from previously conducted clinical trials examined in 3 publications. The studies showed low distant recurrence rates in patients classified as low risk with the test. A reclassification result suggested that the test may offer little improvement over clinical predictors alone. Clarity about how the test would inform clinical practice is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

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SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

Guidelines from the National Comprehensive Cancer Network (NCCN; v.2.2017)[2] recommend the use of the 21-gene reverse transcriptase polymerase chain reaction (RT-PCR) assay for determining the use of adjuvant chemotherapy in patients with the following tumor characteristics:

- Hormone receptor–positive;
- Human epidermal growth factor receptor 2 (*HER2*)–negative;
- Ductal, lobular, mixed, or metaplastic histology;
- "pT1, pT2, or pT3 stage; and pN0 or pN1mi (≤2 mm axillary node metastasis)";
- Tumor >0.5 cm.

The guidelines also state: "The 21-gene RT-PCR assay recurrence score can be considered in select patients with 1 to 3 involved ipsilateral axillary lymph nodes to guide the addition of combination chemotherapy to standard hormone therapy. A retrospective analysis of a prospective randomized trial suggests that the test is predictive in this group similar to its performance in node-negative disease."

Further, the NCCN guidelines state: "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."

Other tests mentioned and studies reviewed in the NCCN guidelines included MammaPrint and Prosigna. NCCN guidelines state that "Other prognostic multigene assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy."

American Society of Clinical Oncology

In 2017, the American Society of Clinical Oncology updated its evidence-based guidelines on the use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer.[67] Table 1 shows the gene expression profiling biomarkers found to have demonstrated clinical utility to guide decisions on the need for adjuvant systemic therapy in women with early-stage invasive breast cancer and known estrogen and progesterone and *HER2* status. The guidelines did not endorse any test for decision-making to determine the length of tamoxifen treatment.

Table 1 Guidelines for Estrogen and Progesterone Receptor–Positive and *HER2*-Negative Breast Cancer

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

Test	Recommendation	QOE	SOR
	with other clinicopathologic variables, to guide decisions on adjuvant systemic therapy		
Node-positive (1-3 nodes)			
MammaPrint	Clinician may use the 70-gene assay to guide decisions on adjuvant systemic therapy in women with high clinical risk per MINDACT categorization	High	Moderate

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

European Group on Tumor Markers

In 2017, the European Group on Tumor Markers updated its guidelines on the clinical use of biomarkers in breast cancer.[68] Table 2 summarizes guidelines on the use of biomarkers in patients with invasive breast cancer.

Table 2 Guidelines on the Use of Biomarkers in Patients with Invasive Breast Cancer

Test	Recommendation	LOE	SOR
Oncotype DX	For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy in patients with ER-positive/HER2-negative, lymph node-negative and lymph node-positive (1 to 3 nodes) disease	1B	A
MammaPrint	For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy to patients with ER-positive/HER2-negative, lymph node-negative and lymph node-positive (1 to 3 nodes) disease	1A	A
Prosigna	For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy to patients with ER-positive/HER2-negative, lymph node-negative and lymph node-positive (1 to 3 nodes) disease	1B	A
EndoPredict	For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy to patients with ER-positive/HER2-negative, lymph node-negative and lymph node-positive (1 to 3 nodes) disease	1B	A
Breast Cancer Index	For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy in patients with ER-positive/HER2-negative, lymph node-negative disease	1B	A

ER: estrogen receptor; *HER2*: human epidermal growth factor receptor 2; LOE: level of evidence; SOR: strength of recommendation.

St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer

The 2015 St. Gallen expert panel focused on "providing a practical approach to the allocation of available therapies" based on "tumor factors … such as hormone receptors and HER2 status, and the metastatic potential, as reflected in measures of proliferation and anatomic extent of disease [and p]atient factors [such as] menopausal status, age, comorbidity, and patient preference."[69]

> "Oncotype DX®, MammaPrint®, PAM-50 ROR® score, EndoPredict®, and the Breast Cancer Index® were all considered usefully prognostic for years 1-5. Beyond 5 years, the Panel was divided almost equally on the prognostic value of Oncotype DX® … EndoPredict® … and the Breast Cancer Index…. PAM50 ROR® score was agreed to be clearly prognostic beyond 5 years, and a clear majority rejected the prognostic value of MammaPrint® in this time period. Only Oncotype DX® commanded a majority in favor of its value in predicting the usefulness of chemotherapy."

The Panel noted that threshold values for decision-making about cytotoxic chemotherapy in patients with luminal disease had not been established for any of the tests. "Multi-parameter molecular assays are expensive and therefore unavailable in much of the world."[69]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

In November 2014, Palmetto GBA issued a local coverage determination for the Breast Cancer Index.[70] Effective October 1, 2015, the policy limits coverage of the Breast Cancer Index to patients who meet the following criteria:

- "Post-menopausal female with non-relapsed, ER+ [estrogen receptor] breast cancer; and
- Is lymph node negative, and
- Is completing 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)"

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POLICY HISTORY

Date	Action	Description
December 2011	New Policy	
December 2012	Policy Update	Policy updated with literature search; rationale revised, references updated, no change in policy statement.
June 2013	Policy Update	Policy updated with literature search; several new references added.

		Policy statement revised to include addition of bilateral disease as investigational, use of Oncotype testing is investigational for women with DCIS, revise MammaPrint to be not medically necessary and add NexCourse Breast IHC4 as investigational.
September 2015	Policy Update	Policy updated with literature review. References 2, 15-16, 26-33, 37, 39, 43, 44, 47-50, 53-55, 62-67, 74, 76, 77 85-88, 90, 92-98, 102-105, 108-109, 117, 121-122, and 126 added references 1, 12, 106 and updated. Policy statement changed to include newer assays BreastPRS, EndoPredict™, BluePrint® and TargetPrint® as investigational. Policy statement on PAM50 updated to Prosigna™. Policy statement added that the use of gene expression assays in men with breast cancer is considered not medically necessary.
March 2017	Policy Update	Policy updated with literature review through October 10, 2016. Reorganized by indication rather than test. References 7, 11, 14-16, 31, and 43 added; several references removed. Policy statement added that Breast Cancer Index, EndoPredict and Prosigna are medically necessary for same indication as Oncotype. Other statements revised to reflect these tests investigational for other indications.
December 2017	Policy Update	Policy updated with literature review through March 21, 2017 for indications 6-9 and 11-14 only. References 1, 6, 8-12, 18-24, 37-42, and 45-50 were added. Policy statements unchanged
March 2018	Policy Update	Policy updated with literature review through September 11, 2017; references 34, 41, 45, 53, and 55-57 were added. Policy statements unchanged.