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

Policy # 00211
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of the 21-gene RT-pcr assay (i.e., Oncotype DX™)‡ to determine recurrence risk for deciding whether or not to undergo adjuvant chemotherapy in women with breast cancer to be **eligible for coverage**.

Patient Selection Criteria
Coverage eligibility for the use of 21-gene RT-pcr assay (i.e., Oncotype DX) to determine recurrence risk for deciding whether or not to undergo adjuvant chemotherapy in women with breast cancer will be considered when ALL of the following criteria are met:

- Unilateral, non-fixed 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 0.6–1 cm with moderate/poor differentiation or unfavorable features OR tumor size greater than 1 cm; 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 6 months following diagnosis, since the value of the test for making decisions regarding delayed chemotherapy is unknown.

Note: The 21-gene RT-pcr Oncotype DX should only be ordered after surgery and subsequent pathology examination of the tumor have been completed. 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.

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When Services Are Considered Investigational
Note: Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers all other indications for the 21-gene RT-PCR assay (i.e., Oncotype DX) to be **investigational.***

Based on review of available data, the Company considers the use of other gene expression assays (e.g., MammaPrint, Mammostrat, the THEROS Breast Cancer Index℠‡, the BreastOncPx, or PAM50 Breast Cancer Intrinsic Classifier) ‡ for any indication is considered to be **investigational.***

Background/Overview

Laboratory tests have been developed that detect the expression, via messenger RNA (mRNA) or protein, 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 post-surgical management.

For women with early-stage breast cancer, adjuvant chemotherapy provides the same proportional benefit regardless of prognosis. However, the absolute benefit of chemotherapy depends on the baseline risk of recurrence. For example, women with the best prognosis have small tumors, are estrogen-receptor-positive, and lymph node negative. These women have an approximately 15% baseline risk of recurrence; approximately 85% of these patients would be disease free at 10 years with tamoxifen treatment alone and could avoid the toxicity of chemotherapy, if they could be accurately identified. Conventional risk classifiers estimate recurrence risk by considering criteria such as tumor size, type, grade, and histologic characteristics; hormone receptor status; and lymph node status. However, no single classifier is considered a gold standard, and several common criteria have qualitative or subjective components that add variability to risk estimates. As a result, more patients are treated with chemotherapy than can benefit. Better predictors of baseline risk could help women, who prefer to avoid chemotherapy if assured that their risk is low, make better treatment decisions in consultation with their physicians.

Recently, several groups have identified panels of gene expression markers ("signatures") that appear to predict the baseline risk of breast cancer recurrence after surgery, radiation therapy, and endocrine therapy (for hormone-receptor-positive tumors). Five gene expression tests are commercially available in the U.S.: Oncotype DX † (a 21-gene reverse transcriptase-polymerase chain reaction [RT-PCR] assay; Genomic Health), the 70-gene signature MammaPrint®‡ † (Agendia), Mammostrat®‡ † Breast Cancer Test (Clarient Diagnostic Services), the Breast Cancer Index, a combination of the Molecular Grade Index (MGI) and the HOXB13:IL17BR Index (bioTheranostics), the BreastOncPx™‡ †(Breast Cancer Prognosis Gene Expression Assay; LabCorp), and the PAM50 Breast Cancer Intrinsic Classifier (ARUP National Reference Laboratory). If these panels are more accurate than current conventional classifiers, they could be used to aid chemotherapy decision making, when current guidelines do not strongly advocate its use, without negatively affecting disease-free and overall survival (OS) outcomes.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
All tests except MammaPrint are provided as laboratory-developed tests (LDTs) in Clinical Laboratory Improvement Act (CLIA)-licensed laboratories operated by each company. These LDTs have not been cleared by the FDA; to date, FDA clearance is not required.

MammaPrint has received 510(k) clearance for marketing by the FDA. All U.S. tests are performed at the CLIA-licensed Agendia clinical laboratory.

Centers for Medicare and Medicaid Services (CMS)
The Local Coverage Determination (Northern California) for Oncotype DX states that "The Oncotype DX test is covered for patients with estrogen-receptor positive, node-negative carcinoma of the breast, for patients with estrogen receptor positive micrometastases of carcinoma of the breast, and for patients with estrogen positive breast carcinoma with 1-3 positive nodes." Results of the Oncotype DX test "are expected to play a significant role in management of the patient." In addition, the test is not considered reasonable and necessary for care when more than six months have elapsed since diagnosis" because the association of the test with outcomes of delayed chemotherapy are not known.

Because all Oncotype DX tests are performed in the Genomic Health clinical laboratory in northern California, the local coverage determination is a de facto national coverage determination.

Rationale/Source

In 2005, a TEC Assessment summarized the evidence for 4 different gene expression profiling assays that were intended for use in identifying those patients at low risk of recurrence for whom adjuvant chemotherapy can be avoided. These were the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) Oncotype DX assay, the 70-gene MammaPrint, the 76-gene "Rotterdam signature" (Veridex), and a 41-gene signature reported by Ahr et al. The TEC Assessment concluded that because published evidence supporting clinical utility was not available, the evidence for all of the gene expression panels was insufficient to permit conclusions.

In 2008, the original TEC Assessment was updated and limited to evaluation of the 3 gene expression profiles commercially available in the United States at that time (Oncotype DX, MammaPrint, and a new test called the Breast Cancer Gene Expression Ratio). The objective of the updated assessment was to determine for patients with early stage, node-negative breast cancer, whether the use of gene expression profiling improves outcomes when used to decide if risk of recurrence is low enough to forego adjuvant chemotherapy, compared to conventional risk assessment tools. The Assessment concluded that the evidence for the 21-gene expression assay (Oncotype DX) met the TEC criteria but that the evidence for the other two assays did not.

In 2010, a TEC Assessment addressed the use of the 21-gene expression assay (Oncotype DX) in lymph node-positive breast cancer patients for the same indications as in the 2005 and 2008 Assessments. The

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Assessment concluded that use of the 21-gene expression profile for selecting adjuvant chemotherapy in patients with lymph node-positive breast cancer did not meet the TEC criteria.

This policy evidence review is based on the above TEC Assessments and on published evidence related to the assays listed in the Background/Overview.

Oncotype DX
Description
The initial indications for the 21-gene expression profile (Oncotype DX) provided by Genomic Health were newly diagnosed breast cancer patients with stage I or II disease that is node-negative and estrogen-receptor (ER)-positive, who would be treated with tamoxifen. Primary validation studies enrolled node-negative patients; this indication is reviewed first. More recently, Genomic Health has expanded their indication to include all stage II disease (tumor $\leq$ 2 cm with spread to axillary lymph nodes or 2-5 cm without lymph node involvement); this indication for lymph node-positive disease will be reviewed separately.

Results from the Oncotype DX 21-gene expression profile are combined into a recurrence score (RS). Based on a study of analytic validity, tissue sampling rather than technical performance of the assay is likely to be the greatest source of variability in results. The 21-gene expression profile was validated in studies using archived tumor samples from subsets of patients enrolled in already completed randomized controlled trials (RCTs) of early breast cancer treatment. Patients enrolled in the trial arms from which specimens were obtained had primary, unilateral breast cancer with no history of prior cancer and were treated with tamoxifen; tumors were ER-positive, most were human epidermal growth factor receptor 2 (HER2)-negative, and in the case of at least 1 trial multifocal tumors were excluded.

Lymph Node-negative Patients
Studies delineating the association between the 21-gene RS and recurrence risk are shown in the Table. Results indicate strong, independent associations between the RS and distant disease recurrence or death from breast cancer. In secondary reclassification analyses of the Paik et al. data, patient risk levels were individually classified by conventional risk classifiers, then re-classified by Oncotype DX. Oncotype DX adds additional risk information to the conventional clinical classification of individual high-risk patients and identifies a subset of patients who would otherwise be recommended for chemotherapy but who are actually at lower risk of recurrence (average 7–9% risk at 10 years; upper 95% confidence interval [CI] limits, 11–15%). The analysis does not indicate significant erroneous reclassification given known outcomes. Thus, a woman who prefers to avoid the toxicity and inconvenience of chemotherapy and whose Oncotype DX RS value shows that she is at very low risk of recurrence might reasonably decline chemotherapy. The lower the RS value, the greater the confidence the woman can have that chemotherapy will not provide net benefit; outcomes are improved by avoiding chemotherapy toxicity.

An additional study, in which samples from a RCT of ER-positive, node-negative breast cancer patients treated with tamoxifen versus tamoxifen plus chemotherapy were tested by Oncotype DX, provides supportive evidence. RS high-risk patients derived clear benefit from chemotherapy, whereas the average

benefit for other patients was statistically not significant, although the confidence intervals were wide and included the possibility of a small benefit.

TEC Assessment
The 2008 Assessment concluded that the 21-gene RT-PCR assay Oncotype DX meets criteria for women similar to those in the validation studies, i.e. women younger than 70 years of age (or with a life expectancy greater than 10 years), with unilateral, non-fixed, ER-positive, node-negative (by full axillary dissection) carcinomas, who are treated with surgery (mastectomy or lumpectomy), radiation therapy, and tamoxifen. In 1 trial, patients in the experimental arm were also treated with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or myelofibrosis (MF) chemotherapy. Most (92%) patients were negative for HER2.

Because clinical care for breast cancer patients has evolved since the original trials from which archived samples were acquired for assay validation, differences in evaluation and treatment regimens were considered. It was concluded that the 21-gene Oncotype DX meets the TEC criteria for the following women with node-negative breast cancer:

- Those receiving aromatase inhibitor (AI)-based endocrine therapy instead of tamoxifen therapy. AI-based therapy would likely reduce recurrence rates for all RS risk groups. Thus, if a patient declined chemotherapy today on the basis of a low-risk RS (risk categories defined by outcomes with tamoxifen treatment), the even lower risk associated with AI treatment would not change that decision. This has been confirmed in the prospectively planned and blinded analysis of samples from the completed Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trial, which evaluated 5 years of anastrozole, tamoxifen, or the combination of both in postmenopausal women with localized breast cancer. The relative risk reduction for anastrozole compared with tamoxifen was similar across different values of the RS, and the risk for distant recurrence in RS low-risk patients was as low or lower than reported in the original validation studies.
- Those receiving anthracycline-based chemotherapy instead of CMF. The type of chemotherapy does not change the interpretation of the Oncotype DX risk estimate. In addition, a recent meta-analysis indicates that anthracyclines do not improve disease-free or OS in women with early, HER2-negative breast cancer, and therefore may not be prescribed in this population.
- Lymph nodes with micrometastases are not considered positive for purposes of treatment recommendations. Current practice largely involves a detailed histologic examination of sentinel lymph nodes, allowing for the detection of micrometastases (less than 2 mm in size).
- Those whose tumors are ER-positive or PR-positive. Only ER-positive women were enrolled in Oncotype DX validation studies, whereas current clinical guidelines include either ER or PR positivity in the treatment pathway for hormone receptor-positive women with early breast cancer. Recent studies show that ER-negative, PR-positive patients also tend to benefit from endocrine therapy.

Several papers related to the use of the 21-gene profile have been published since the 2008 Assessment. Some of these papers will be briefly mentioned. Toi et al. confirmed the clinical validity of the 21-gene profile in a Japanese population of ER-positive, lymph node-negative patients with similar results for risk of distant recurrence in the 3 RS categories as in the original validation studies. Tang et al. compared the

prognostic and predictive utility of RS and Adjuvant! in the NSABP B-14 and B-20 trial patients. An Adjuvant! Risk Index (RI) was fashioned with cutoff points, allowing a patient risk distribution similar to that of the 21-gene RS. The results of the study demonstrated that the RS and Adjuvant! RI are independent prognostic factors of risk of distant recurrence; in addition, while RS was significantly predictive of chemotherapy benefit, Adjuvant! was not. In a hypothesis-generating study, Mamounas et al. investigated the association between RS and risk for locoregional recurrence (LRR), as opposed to distant recurrence, in patients from the same two NSABP trials. For 895 tamoxifen-treated patients, the 10-year Kaplan-Meier estimate of LRR was 4.3% (95% CI, 2.3-6.3%) for patients with a low RS (< 18), 7.2% (3.4-11.0%) for those with intermediate RS (18-30) LRR, 15.8% (10.4- 21.2%) for those with a high RS (> 30). LRR results were higher for those in all RS groups treated with placebo, and lower for those in all RS groups treated with tamoxifen and chemotherapy. Thus, RS was a significant and independent predictor of LRR along with initial treatment type.

Tzeng et al. examined how women receive and incorporate the results of their 21-gene profiles using mailed survey and chart review. About two thirds of women believed they understood most or all of what they were told about their recurrence risk based on their test results; the majority who experienced test-related distress had intermediate or high estimated recurrence risks by RS result. The objective, recalled, and perceived recurrence risks by women in the study were surprisingly similar, and 95% agreed that the test gave them a better understanding of their treatment options and chances of success. However, about one third of women believed they understood only a moderate amount or less during these discussions. The study was limited in generalizability in that participants were mostly Caucasian, well-educated women who had health insurance and came from urban areas.

Several studies have been published regarding the impact of RS results on chemotherapy recommendations by medical oncologists. In general, these studies report that comparing recommendations made prior to and revised after knowledge of RS results show that decisions change in about 30-40% of patients, most often from endocrine therapy plus chemotherapy to endocrine therapy alone. Some view these as evidence of clinical utility because more patients avoid the toxicity of chemotherapy; however there are no patient outcomes attached to these studies; outcomes are assumed based on the original assay clinical validity evidence. In addition, none of the studies formalize and describe the way in which information is delivered to the patient, nor do they evaluate how patient preferences are incorporated into the final treatment decision. Lo et al. conducted a prospective multicenter study that examined both physician and patient treatment selection, as well as the impact of the RS result on patients' anxiety, quality of life, and satisfaction with choice of treatment but did not address the issue of whether results were described using a similar format for all patients so that they all had as close to the same information base as possible.

Ongoing trials
Limitations of the current evidence, such as confirmation of optimal RS cutoff values for tamoxifen-treated and separately for AI-treated patients and recommendations for patients with intermediate RS values, are likely to be answered by the results of the ongoing Trial Assigning Individualized Options for Treatment (Rx), also known as TAILORx.

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Additional applications
Based on a study published in May 2008 that compared the Oncotype DX ER and PR results to traditional IHC results, Genomic Health is now including the quantitative ER and PR component results in the Oncotype DX 21-gene profile report. The study reported 90% or better concordance between the two assays but that quantitative ER by Oncotype DX was more strongly associated with disease recurrence than the IHC results. However, ER and PR analysis is traditionally conducted during pathology examination of all breast cancer biopsies, whereas Oncotype DX is indicated only for known ER-positive tumors, after the pathology examination is complete, the patient meets specific criteria, and patient and physician are considering preferences for risk and chemotherapy. Thus, Oncotype DX should not be ordered as a substitute for ER and PR IHC. Additionally, accepted guidelines for ER and PR testing outline standards for high-quality IHC testing and do not recommend confirmatory testing; thus the 21-gene RS should not be ordered to confirm ER/PR IHC results. Similarly, guidelines for HER2 testing specify IHC and/or fluorescence in situ hybridization (FISH) methods. Although the HER2 component of the 21-gene assay has been shown to strongly correlate with FISH results. The 21-gene assay should not be ordered to determine or confirm HER2.

The 2008 TEC Assessment also evaluated studies of Oncotype DX for use in predicting response to specific chemotherapy regimens and found the evidence insufficient for conclusions. These studies were reviewed, and the search was updated for this policy review; no published studies were found that changed these conclusions.

Table. Summary of Oncotype DX RS and recurrence risk studies.

Study Study Type	Total N	Study Objective	Results		
Paik et al 2004a TAM arm of NSABP B-14 RCT	668	Predict recurrence	RS risk Low (< 18) Intermed (18-30) High (> 31) All	% of patients 51 22 27 100	K-M distant recurrence at 10 yr, % (95% CI) 6.8 (4.0-9.6) 14.3 (8.3-20.3) 30.5 (23.6-37.4) 15 (12.5-17.9)
Paik et al 2004b Additional analysis of Paik et al 2004a data	668	Reclassification study; determine incremental risk compared to conventional classifier	Risk classification by NCCN[1] Low (8%) High (92%)	Risk re-classification Oncotype DX Low Intermed High Low Intermed High	N % DRF at 10 yr (95% CI[2]) 38 100 (NR) 12 80 (59-100) 3 56 (13-100) 301 93 (89-96) 137 86 (80-92) 178 70 (62-77)

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Bryant 2005 Additional analysis of Paik et al 2004a data	668	Reclassification study; determine incremental risk compared to conventional classifier	Risk classification by Adjuvant! Online[1] Low (53%) Int-High (47%)	Risk re-classification by Oncotype DX Low Int-High Low Int-High	N 214 140 120 194	% recurrence at 10 yr (95% CI[2]) 5.6 (2.5-9) 12.9 (7-19) 8.9 (4-14) 30.7 (24-38)
Habel et al 2006 Case control	255 ER+ TAM+; 361 ER+ TAM-	Predict mortality	RS risk Low (< 18) Int (18-30) High (> 31)	10-yr absolute risk of death, % (95% Cl) ER+, TAM Treated 2.8 (1.7-3.9) 10.7 (6.3-14.9) 15.5 (7.6-22.8)	ER+, No TAM 6.2 (4.5-7.9) 17.8 (11.8-23.3) 19.9 (14.2-25.2)	

Abbreviations: DRF, distant recurrence-free; ER, estrogen receptor; N, total number of patients; NR, not reported; RS, Oncotype DX recurrence score; K-M, Kaplan Meier; NSABP, National Surgical Adjuvant Breast and Bowel Project; RCT, randomized controlled trial; TAM, tamoxifen; NCCN, National Comprehensive Cancer Network (2004); Int/Intermed, Intermediate.

[1]Percentages are percent of total N.

[2]Estimated from graphs. Note that different outcomes were reported between Paik et al. 2004b and Bryant 2005 and could not be converted to similar outcomes with confidence intervals.

MammaPrint

MammaPrint is a prognostic test for women younger than 61 years with ER-positive or ER-negative, lymph node-negative breast cancer. The 2008 TEC Assessment reviewed available studies and found insufficient evidence to determine whether MammaPrint is better than conventional risk assessment tools in predicting recurrence. Limited technical performance evaluation of the commercial version of the assay suggests good reproducibility. Recurrence rates of patients classified as low risk in available studies were 15–25%, likely too high for most patients and physicians to consider forgoing chemotherapy. Similarly, in one study, after Adjuvant! risk classification, patients reclassified as low risk by the 70-gene signature in either Adjuvant! risk group had 10-year DFS rates of 88–89%, with lower confidence limits of 74–77%. Patients reclassified as high risk had 10-year DFS rates of 69%, with lower confidence limits of 45–61% and upper confidence limits of 76–84%; receiver operating characteristic (ROC) analysis suggests only a small improvement with MammaPrint classification compared to a conventional classifier.

Because initial studies had been conducted on samples from younger patients (age younger than 61 years), Wittner et al. studied a cohort of 100 lymph node-negative patients with a median age of 62.5 years and a median follow-up of 11.3 years. Twenty-seven low-risk patients by MammaPrint had distant metastasis-free

survival at 10 years of 100%. However, the study was underpowered, and patients were heterogeneous in terms of ER-positivity (73%), endocrine therapy (25%), and chemotherapy (23%) making conclusions difficult.

Two studies of MammaPrint were published in 2009. One small (n = 123) study of lymph node-negative patients younger than 55 years, 76% with ER-positive tumors, who received variable treatment for early-stage breast cancer, reported that the 70-gene signature was significant in multivariate analyses for prognosis. However, the small study size and small number of events precludes an adequate statistical analysis. This study also updated results of 151 node-negative patients from the validation study, reporting distant metastasis (as first event) free percentage as 86 $\pm$ 5% in good prognosis signature patients.

Mook et al. studied 241 patients with 1-3 positive nodes and primarily ER-positive, HER2-negative tumors treated variably. The 70-gene signature was a significant predictor of outcome and reclassification analysis using Adjuvant! Online vs. MammaPrint. Results showed significant additional discrimination of outcomes by the gene signature, but all were confounded by heterogeneous patient treatment. This study also updated the results of 106 patients with 1-3 positive nodes from the validation study, reporting 98% (95% CI, 94-100%) 10-year breast cancer-specific survival for good prognosis signatures vs. 64% (52-76%) for poor prognosis signatures; adjusted hazard ratio (HR): 3.63 (0.88–14.96), p = 0.07. Based on these results, the ongoing MINDACT trial of MammaPrint was enlarged to include patients with 1-3 positive lymph nodes.
Studies published in 2010 and 2011 comprise primarily small case series, and pooled re-analyses of subgroups from previously published retrospective studies. A pooled analysis of 964 patients from previously reported studies with pT1 tumors ($\leq$ 2 cm) included 84% with ER-positive tumors, 68% with HER2-negative tumors (no HER2 information on 23%), 27% with node-positive disease, 68% given no adjuvant treatment, and the rest treated variably. In these patients, overall distant metastasis-free survival at 10 years was 87% (95% CI: 84-91%) for good prognosis patients and 72% (66-78%) for poor prognosis patients. The hazard ratio was 2.70 (95% CI: 1.88–3.88, p<0.001). Breast cancer-specific survival was slightly higher for the good prognosis group at 91% (87-95%), and the same for the poor prognosis group. Results are confounded by nodal status, HER2 status, and adjuvant therapy also being significant predictors of the outcome.

Kunz conducted a pooled re-analysis of a subgroup of patients aged 35-55 years from previously published retrospective studies of the 70-gene signature. Patients were 75% ER-positive, 45% node-positive; 60% were untreated and the rest treated variably. The 70-gene signature categorized 39% of patients as good prognosis; for these patients the 10-year time to distant metastasis was 88% (95% CI: 84–92%). Kunz et al. also prospectively evaluated the use of the 70-gene signature in 54 premenopausal patients; of these 19% were either lost in transit or had insufficient tumor in the tissue sample. Of the remaining samples, 66% were classified good prognosis compared to Adjuvant! Online (43%) or St Gallen (% good, 77% intermediate prognosis). Outcomes were not available. Bighin et al. also reported difficulties in that nearly 25% of 21 prospectively studied patients were not assessable by the 70-gene signature and that results lead to a change in clinical decision in fewer than 20% of cases.

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Mook et al. retrospectively evaluated 148 consecutive, node-negative, post-menopausal patients, nearly all of whom had ER-positive tumors; only 18% received 2 years of adjuvant tamoxifen and none chemotherapy. For the 61% with good prognosis, 5-year distant metastasis-free survival (DMFS) probability was 93% (95% CI, 87-99%) whereas for those with poor prognosis DMFS was 72% (60-84%). The authors reported on concordance with Adjuvant! Online, but did not conduct a net reclassification analysis.

Finally, Retel et al. reported a cost-effectiveness analysis that simulated the course of events in a hypothetical cohort of 1,000 patients aged 50 years with early, operable node-negative, ER-positive breast cancer, who are treated with 2.5 years of tamoxifen and 2.5 years of an aromatase inhibitor. The 70-gene signature was compared with Adjuvant! Online and St Gallen clinicopathologic classifiers. While all three strategies were clinically equally effective, St Gallen was more costly and the 70-gene signature was most cost-effective when quality-adjusted life-years were taken into account.

The studies of the 70-gene signature continue to suffer from confounding in heterogeneous sample populations. Pooled re-analyses of subpopulations may control for one variable (e.g. nodal status), but confounding remains from other variables (e.g. treatment heterogeneity). Results for the 70-gene signature good prognosis patients have confidence intervals that extend into ranges that likely confer too much risk for patients and providers in the U.S. Because the test result is not a continuous numerical result, patients cannot view their result within the spectrum of good prognosis results and adjust their preferences accordingly.

Breast Cancer Index
The Breast Cancer Index is a simultaneous assessment of HOXB13:IL17BR (H/I) Index and the MGI[SM] (Molecular Grade Index). The 2008 TEC Assessment reviewed available studies for the original component assays. There was insufficient evidence to determine whether the H/I Ratio is better than conventional risk assessment tools in predicting recurrence. Ten-year recurrence rates of patients classified as low risk in available studies were 17–25%, likely too high for most patients and physicians to consider forgoing chemotherapy. The Molecular Grade Index is intended to measure tumor grade using the expression of 5 cell cycle genes and to provide prognostic information in ER-positive patients regardless of nodal status.

Ma et al. evaluated MGI along with H/I in 93 patients with lymph node–negative tumors who received adjuvant hormone therapy and found that each index modified the other's predictive performance. High MGI was associated with significantly worse outcome only in patients with high H/I and vice versa. When the H/I Ratio and MGI were categorically combined into a single predictor, the estimates of 10-year distant metastasis-free survival were 98% (95% CI, 96-100%), 87% (77-99%), and 60% (47-78%) for the low, intermediate, and high-risk groups, respectively.

Jerevall et al. combined the H/I Ratio and MGI into a continuous risk model using 314 ER-positive, node-negative postmenopausal patients from the tamoxifen-only arm of an RCT. The continuous model was also categorized, resulting in proportions of low, intermediate, and high-risk patients similar to those reported in the Ma et al. study. This continuous predictor was tested in patients from the no adjuvant treatment arm (n = 274) of the same clinical trial, with estimates of rates of distant metastasis at 10 years in the low,

intermediate, and high risk groups of 8.3% (95% CI: 4.7–14.4), 22.9% (14.5–35.2) and 28.5% (17.9–43.6), respectively. The estimates of breast cancer-specific death were 5.1% (95% CI: 1.3–8.7), 19.8% (10.0–28.6), and 28.8% (15.3–40.2). An independent population of otherwise similar but tamoxifen-treated patients was not tested. There are no reclassification studies of comparison with conventional risk classifiers; thus, clinical utility in a population likely to be treated with tamoxifen is unclear.

Mammostrat Breast Cancer Test
Mammostrat is an immunohistochemistry (IHC) test intended to evaluate risk of breast cancer recurrence in postmenopausal, node-negative, ER-positive breast cancer patients who will receive endocrine therapy and are considering adjuvant chemotherapy. The test employs 5 monoclonal antibodies to detect gene expression of proteins biologically independent of each other and not involved in cell proliferation, hormone receptor status, or growth/differentiation, thus potentially allowing integration with clinically routine biomarkers. A proprietary diagnostic algorithm is used to calculate a risk score and to classify patients into high-, moderate-, or low-risk categories.

One published study described the development of the assay but provides no information on technical performance (analytic validity). In a validation study in an independent cohort, a multivariable model predicted 50%, 70%, and 87% 5-year DSF for patients classified as high, moderate, and low prognostic risk, respectively, by the test results (p = 0.0008). An additional study of the same trial samples used for Oncotype DX validation (NSABP B-14 and B-20 trials) found that among patients with early, node-negative breast cancer treated only with tamoxifen, those stratified by Mammostrat into low-, moderate-, and high-risk groups had recurrence-free survival estimates of 85%, 85%, and 73%, respectively. Both low- and high-risk groups benefited significantly from chemotherapy treatment, but high-risk patients benefited to a greater degree. The moderate-risk group was not well-separated from the low-risk group and thus, moderate-risk results do not appear to provide clinically useful information. A test for an interaction between chemotherapy and the risk group stratification was not significant (p = 0.13).

Bartlett et al. used Mammostrat on 1,540 of 1,812 patient samples from a consecutive cohort for which minimum 9-year outcomes were available. The tested samples were from tamoxifen-treated patients; 568 of these were from node-negative patients treated only with tamoxifen and whose tumors were ER-positive. In the latter group, the distant recurrence rates at 10 years for low-, moderate-, and high-risk patients were 7.6% (95% CI, 4.6-10.5%), 16.3% (10.0-22.6%), and 20.9% (12.3-29.5%) respectively. In multivariable analysis, Mammostrat was not a significant predictor of recurrence-free survival in node-negative, ER-positive patients treated only with tamoxifen. However, when all patients (24% node-positive, 20% tumors > 2.0 cm, 18% ER-negative, and 46% treated with chemotherapy) with complete Mammostrat data (n = 1,300) were included in a multivariable analysis, Mammostrat scores were independent predictors of recurrence-free survival (p = 0.0007). In exploratory analyses of various subpopulations (e.g. node-negative vs. node-positive, ER-negative), Mammostrat appeared to perform similarly in terms of identifying risk groups. However, numbers of subsets were small.

There are no published reclassification studies of comparison with conventional risk classifiers.

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BreastOncPx
The BreastOncPx test is an RT-PCR test performed on formalin-fixed, paraffin embedded tissue that measures the gene expression of 14 genes associated with key functions such as cell cycle control, apoptosis, and DNA recombination and repair. The results are combined into a metastasis score, which is reported to be associated with the risk of distant metastases in patients who are node-negative and estrogen-receptor positive.

Tutt et al. published information on the development and validation of the test; no information on analytic validity was provided. In order to develop a gene signature that was completely prognostic for distant recurrence and not confounded by treatment prediction, samples from untreated patients with early breast cancer were used. The training set (n = 142) was derived from a cohort diagnosed with lymph node-negative, stage T1 and T2 breast cancer from 1975 to 1986; ER-positive samples from patients who had had no systemic treatment were selected for analysis. Fourteen genes were eventually selected as most prognostic of time-to-distant metastasis and were given equal weighting in a summary metastasis score (MS). Using a single cutoff, patients are separated into high- and low-risk groups.

The 14-gene signature was validated on ER-positive samples (n = 279) from a separate cohort of patients diagnosed with lymph node-negative primary breast cancer between 1975 and 2001. The estimated rates of distant metastasis-free survival were 72% (95% CI: 64-78%) for high-risk patients and 96% (95% CI: 90-99%) for low-risk patients at 10 years' follow up. Overall 10-year survival for high and low risk patients was 68% (95 CI: 61% to 75%) and 91% (95% CI: 84 to 95%), respectively. After adjusting for age, tumor size, and tumor grade in a Cox multivariate analysis, the HRs for distant metastasis-free survival for the high- versus low-risk group were 4.02 (95% CI: 1.91-8.44) and 1.97 (95% CI: 1.28 to 3.04) for distant metastasis-free survival and overall survival, respectively. However, this difference in risk between groups was not maintained when the analysis was restricted to patients with tumors larger than 2 cm (p value for interaction 0.012).

ROC analysis of the continuous MS for distant metastasis and for death at 10 years, compared to Adjuvant! resulted in slightly higher area under the curves (AUCs) for the MS in each case: 0.715 vs. 0.661 for distant metastases, and 0.693 vs. 0.655 for death. MS was not added to Adjuvant! and compared to Adjuvant! alone. No reclassification analysis was conducted.

PAM50 Breast Cancer Intrinsic Classifier
The initial development of the PAM50 breast Cancer Intrinsic Classifier was reported by Parker et al. The authors developed a qRT-PCR test based on a panel of 50 genes to identify the breast cancer "intrinsic" subtypes luminal A, luminal B, HER2-enriched, and basal-like, and to generate risk-of-relapse scores in node-negative patients who had not had systemic treatment for their cancer. In an independent test set, the test using three categories of risk (low, intermediate, and high) was significantly prognostic (Log-rank p = 0.0002).

Nielsen et al. compared the PAM50 classifier with standard clinicopathologic factors as represented by Adjuvant! Online and with models based on IHC for biomarkers of intrinsic subtypes. The study used

samples from patients diagnosed between 1986 and 1992 with ER-positive breast cancer, either higher-risk (e.g. with lymphovascular invasion) node-negative or node-positive disease, and treated with 5 years of tamoxifen but no adjuvant chemotherapy. In the node-negative population, Adjuvant! Online was inferior to all other biomarker models for predicting recurrence and disease-specific survival. A model including the PAM50 risk of recurrence gene expression signature that also incorporated the influence of proliferation and tumor size identified patients with a greater than 95% chance of remaining alive and disease-free beyond 10 years. A slightly different gene expression model best fit the node-positive population but did not identify a sufficiently low-risk population that adjuvant hormone therapy would likely be considered sufficient.

Because the cohort used to generate the models evaluated in this study was biased toward higher-risk early breast cancers, it is likely not generalizable. Nor did the authors clearly identify a final model for clinical use. Rather, the authors outlined potential additional studies.

Test Comparison Studies
Fan et al. used 5 gene expression classifiers to evaluate a single set of samples from 295 women with stage I or II breast cancer, variable node involvement, and variable endocrine or chemotherapy treatment. The classifiers included the 21-gene Recurrence Score, the 70-gene signature, the H/I ratio, and the intrinsic subtype classifier (similar to the commercially available PAM50). Most highly correlated were the 21-gene Recurrence Score and the 70-gene signature at a Cramer's V of 0.6 (scale 0 to 1 with 1 indicating perfect agreement). More specifically, 81 of the 103 samples with a Recurrence Score of low or intermediate risk were classified as having a low risk 70-gene profile. Restricting the analysis to the 225 ER-positive samples slightly reduced the correlation. The analysis was not further restricted to node-negative patients, the present indication for both tests.

Espinosa et al. compared the 21-gene Recurrence Score (Oncotype DX), the 70-gene signature (MammaPrint), and the 2-gene ratio (H/I Ratio) in 153 patients with ER-positive breast cancer treated with adjuvant tamoxifen. Thirty-eight percent of these patients were node-positive, and 63% were additionally treated with chemotherapy. Distant metastasis-free survival for the Recurrence Score profile was 98% for low-risk patients versus 81% intermediate risk versus 69% high-risk; for the 70-gene signature the estimates were 95% good prognosis versus 66% poor prognosis; and for the 2-gene ratio, 86% favorable versus 70% unfavorable. There was a good correlation between the 21-gene Recurrence-Score and the 70-gene signature (Cramer's V = 0.6). Slightly more variation in distant metastasis-free survival was explained by the combination of the 21-gene Recurrence score and either Adjuvant! Online (25.8$\pm$1.4) or the Nottingham Prognostic Index (NPI; 23.7$\pm$1.5) than by the combination of the 70-gene signature with Adjuvant! Online (23.1$\pm$1.2) or the NPI (22.4$\pm$1.3), but the differences were very small and any combination was significantly better than any test or clinicopathologic classifier alone.

Summary
21-gene Recurrence Score (Oncotype DX):
The assay is supported by strong evidence of clinical validity, i.e., that the RS is strongly associated with risk of distant recurrence in women with breast cancer that is positive for hormone receptors, and negative for HER2. Limited but sufficient evidence supports analytic validity and clinical utility in this population.

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Oncotype DX adds additional risk information to the conventional clinical classification of individual high-risk patients and identifies a subset of patients who would otherwise be recommended for chemotherapy but who are actually at lower risk of recurrence (average 7–9% risk at 10 years; upper 95% CI limits: 11–15%). Thus, a woman who prefers to avoid the toxicity and inconvenience of chemotherapy and whose Oncotype DX RS value shows that she is at very low risk of recurrence might reasonably decline chemotherapy.

70-gene signature (MammaPrint):
A large number of studies of clinical validity, and a few attempting to address the clinical utility of the 70-gene signature have been published. Several studies have pooled and re-analyzed subsets of previously published data in attempts to arrive at more homogeneous sample populations. Nevertheless, the studies of the 70-gene signature continue to suffer from confounding in heterogeneous sample populations. Pooled re-analyses of subpopulations may control for one variable (e.g., nodal status), but confounding remains from other variables (e.g., treatment heterogeneity). Results for the 70-gene signature good prognosis patients have confidence intervals that extend into ranges that likely confer too much risk for patients and providers in the U.S. Because the test result is not a continuous numerical result, patients cannot view their result within the spectrum of good prognosis results and adjust their preferences accordingly.

Mammostrat Breast Cancer Test, Breast Cancer Index, BreastOncPx, Pam50 Breast Cancer Intrinsic Classifier
The available evidence supporting these tests consists of clinical validity data showing that the test is independently and significantly associated with distant recurrence and that the test can identify a lower risk population of women with breast cancer who may not need chemotherapy. In almost all cases, the test is not added to and compared with a standard clinicopathologic classifier such as Adjuvant!, nor were any reclassification analyses reported. The BreastOncPx validation study included an ROC analysis comparing the test with Adjuvant!, but no clear evidence supporting clinical utility was available.

Neither the NCCN, nor the American Society of Clinical Oncology support any indications for the use of MammaPrint, THEROS Breast Cancer Index, or Mammostrat. The St. Gallen guidelines refer to the use of validated, multigene assays in specific situations but do not name any specific assays.

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Code Type	Code
CPT	81599, 84999
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ICD-9 Procedure	No code

Policy History

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09/20/2006 Medical Policy Committee approval

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

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10/03/2007	Medical Director review
10/17/2007	Medical Policy Committee approval. Policy Statements Changed. Oncotype DX eligible for coverage. Not medically necessary statement added.
02/13/2008	Medical Director review
02/20/2008	Medical Policy Committee approval. Policy statement changed to include patient selection criteria. Added 21-gene RT-pcr assay Oncotype DX .
02/04/2009	Medical Director review
02/19/2009	Medical Policy Committee approval. Clarified 6th and 7th criteria bullets. No change to coverage eligibility.
02/04/2010	Medical Policy Committee review
02/17/2010	Medical Policy Implementation Committee approval. No change to coverage.
02/03/2011	Medical Policy Committee review
02/16/2011	Medical Policy Implementation Committee approval. New criteria added.
02/02/2012	Medical Policy Committee review
02/15/2012	Medical Policy Implementation Committee approval. Rationale extensively revised. Coverage eligibility unchanged.
02/07/2013	Medical Policy Committee review
02/20/2013	Medical Policy Implementation Committee approval. Added the BreastOncPx and the PAM50 Breast Cancer Intrinsic Classifier as examples of investigational gene expression assays.
12/12/2013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. "Node negative (lymph nodes with micrometastases (less than 2 mm in size) are considered node negative for this policy statement)" was removed from policy criteria.

Next Scheduled Review Date: 12/2014

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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A. in accordance with nationally accepted standards of medical practice;
B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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