I. Description

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 hormonal therapy (for hormone-receptor-positive tumors) in women with node-negative disease. Five gene expression tests are commercially available in the United States: Oncotype DX™ (a 21-gene RT-PCR assay; Genomic Health), the 70-gene signature MammaPrint® (also referred to as the "Amsterdam signature"; Agendia), Mammostrat™ (Applied Genomics Inc.), the Molecular Grade Index (Aviara MGISM; AviaraDx, Inc.), and the THEROS Breast Cancer IndexSM. 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 outcomes.
II. Criteria/Guidelines

A. Oncotype DX is covered (subject to Limitations/Exclusions and Administrative Guidelines) when all of the following criteria are met:
   1. The patient has unilateral, non-fixed tumor;
   2. The tumor is hormone receptor positive (i.e., ER-positive and/or PR-positive);
   3. The tumor is HER2-negative;
   4. The tumor size is 0.6–1 cm with moderate/poor differentiation or unfavorable features OR tumor size greater than 1 cm;
      a. 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.
   5. Node negative (lymph nodes with micro-metastases less than 2 mm in size are considered node negative);
   6. The patient will be treated with adjuvant endocrine therapy (e.g., tamoxifen).

B. Chemotherapy as a therapeutic option is being considered and will be supervised by the physician ordering the gene profile. 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.

III. Limitations/Exclusions

A. Any other indication for Oncotype DX, except those listed in Criteria/Guidelines is not covered.

B. The use of other gene expression assays (e.g., MammaPrint, Mammostrat, etc.) for any indication does not meet payment determination criteria and is not covered.

IV. Administrative Guidelines

A. Precertification is not required.

B. Documentation supporting the medical necessity should be legible, maintained in the patient's medical record and must be made available to HMSA upon request. HMSA reserves the right to perform retrospective review using the above criteria to validate if services rendered met payment determination criteria.

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<th>CPT Codes</th>
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V. Scientific Background

Oncotype DX
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 <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 progesterone receptor (PR)-positive. Only ER-positive women were enrolled in Oncotype DX validation studies, whereas current clinical guidelines include either ER or progesterone receptor (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.
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.

Lymph node-positive patients

Albain et al. evaluated samples from the Southwest Oncology Group Trial 8814, in which randomized node-positive, ER-positive patients treated with tamoxifen for 5 years were compared to those treated with cyclophosphamide, doxorubicin, fluorouracil (CAF) chemotherapy followed by tamoxifen (CAF-T) for 5 years. Samples were available for determination of RS for 41% (n=148) and 39% (n=219) of the trial arms, respectively.

In this study, 10-year disease-free survival (DFS) and overall survival (OS) outcomes in the tamoxifen study arm differed by RS risk category (p=0.017 and 0.003, respectively), indicating that the RS is prognostic. When the 2 treatment arms were compared within RS risk categories, only patients in the high RS category significantly benefited from the addition of CAF to tamoxifen (for DFS, 42% [tamoxifen] vs. 55% [CAF-T], p=0.033; for OS, 51% [tamoxifen] vs. 68% [CAF-T], p=0.027), suggesting that RS is also predictive of response to chemotherapy.

A multivariable analysis of RS interaction with DFS, adjusted for number of positive nodes, was significant for the first 5 years of follow-up at p=0.029 and remained significant after adjusting for age, race, tumor size, progesterone receptor status, grade, p53, and HER2. However, the interaction was not significant (p=0.15) after adjusting for ER level (ER gene expression is a component of the 21-gene profile). Interaction results were similar for OS.

Dowsett et al. included a separate evaluation of node-positive patients in their examination of the ATAC Trial samples. Of 306 node-positive patients, 243 had 1-3 involved nodes, and 63 patients 4 or
more; these were not evaluated separately. Rates of distant recurrence at 9 years were 17% (95% CI, 12-24%), 28% (20-39%), and 49% (35-64%), respectively. It is not clear that the risk of distant recurrence in low-risk RS patients would be sufficiently low to forgo the choice of chemotherapy. The authors note that their study “did not directly evaluate the value of RS in predicting the benefit of chemotherapy.” Goldstein et al. evaluated samples from the Eastern Cooperative Oncology Group E2197 trial, which included patients with 0-3 positive lymph nodes and operable tumor greater than 1cm in size. Patients were randomly assigned to doxorubicin plus cyclophosphamide or docetaxel plus 5 years of endocrine therapy, but outcomes were not significantly different for the study arms. A case-control study of samples from this trial found that low-risk RS patients with 0-1 positive nodes had a recurrence risk of 3.3% (95% CI, 2.2-5%), and low-risk patients with 2-3 positive nodes had a recurrence risk of 7.9% (4.3-14.1%). RS was also a significant predictive of risk regardless of nodal status. RS could not be evaluated with respect to predicting chemotherapy benefit.

A previous study by Chang et al., not designed to validate the 21-gene profile, reported that in women with locally advanced breast cancer treated with neoadjuvant docetaxel (n=97), a complete response was more likely in those with a high RS (p=0.008). Gianni et al. studied 93 patients with locally advanced breast cancer who received neoadjuvant taxane chemotherapy, then post-surgery CMF treatment and tamoxifen (if ER-positive). The authors reported that pathological complete response was more likely in patients with high RS results than with low RS results (p<0.01).

One study surveyed oncologists who are already ordering the 21-gene profile for lymph node-positive patients to determine the effect of the assay results on treatment recommendations and reported that approximately half changed their recommendations after receiving RS results, with 33% recommending endocrine therapy alone instead of endocrine plus chemotherapy. The majority of the 160 respondents (16% response rate reported being satisfied with the data supporting the use of the assay in node-positive disease. However, medical oncologists who treat breast cancer patients were not surveyed in general, only those who were already using the assay, thus skewing the results. Finally, no outcomes were reported, so the study provided no firm evidence of clinical utility in this population.

Additional studies are necessary before it is possible to confidently withhold currently recommended chemotherapy from lymph node-positive breast cancer patients with low/intermediate RS results. The RxPONDER (Rx for Positive Node, Endocrine Responsive Breast Cancer) trial, lead by the Southwest Oncology Group, will enroll 4,000 women with RS equal to or less than 25 who have early stage, hormone receptor-positive, HER2-negative breast cancer involving one to three lymph nodes. Patients will be randomized to receive either chemotherapy with endocrine therapy or endocrine therapy alone.

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±1.4) or the Nottingham Prognostic Index (NPI; 23.7±1.5) than by the combination of the 70-gene signature with Adjuvant! Online (23.1±1.2) or the NPI (22.4±1.3), but the differences were very small and any combination was significantly better than any test or clinicopathologic classifier alone.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers
In response to requests, input was received from 1 physician specialty society and 4 academic medical centers while this policy was under review in 2008. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. A clear majority of the reviewers agreed with the policy conclusions.

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, negative for HER2, and without lymph node involvement. Limited but sufficient evidence supports analytic validity and clinical utility in this population. 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.
In similar women who are node-positive, the evidence is less clear that the risk of recurrence in low-risk RS patients is sufficiently low or that the benefit of chemotherapy is insufficiently large, to recommend avoiding otherwise currently recommended treatment. Additional studies are necessary and ongoing.

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.

Practice Guidelines and Position Statements

The 2011 National Comprehensive Cancer Network (NCCN) guidelines indicate that Oncotype DX (termed the “21-gene RT-PCR assay”) is an option in breast cancer patients with the following characteristics:

- Hormone receptor-positive;
- HER2-negative;
- Node-negative OR not greater than 2 mm axillary node metastasis; AND
- Size of 0.6–1 cm and moderate/poorly differentiated or unfavorable features OR size larger than 1 cm.

The 2007 American Society of Clinical Oncology (ASCO) guidelines indicate that “In newly diagnosed patients with node-negative, estrogen-receptor positive breast cancer, the Oncotype DX assay can be used to predict the risk of recurrence in patients treated with tamoxifen.” In 2009, the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer “considered the available multigene assays...and concluded that “a validated assay should be taken into account as
an adjunct to high-quality pathology phenotyping” if there was doubt about the clinical decision regarding chemotherapy, but did not name any specific assays.

Neither the NCCN, nor the American Society of Clinical Oncology specifically support any indications for the use of MammaPrint, Mammostrat, Breast Cancer Index, BreastOncPx, or PAM50.

Medicare National Coverage

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.

VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.
VII. References


