**Medical Policy**

**Title:** Gene Expression Assay for Breast Cancer Treatment

**Professional**
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**DESCRIPTION**

For women with early-stage, invasive breast cancer (i.e. cancer extends beyond the basement membrane of the milk ducts into adjacent tissue), 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 invasive breast cancer recurrence after surgery, radiation therapy, and endocrine therapy (for hormone-receptor-positive tumors). Gene expression tests commercially available in the U.S. include: 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 (Clariion Diagnostic Services), the Breast Cancer IndexSM, a combination of the Molecular Grade Index (MGI) and the HOXB13:IL17BR Index (bioTheranostics), the BreastOncPx™ (Breast Cancer Prognosis Gene Expression Assay; LabCorp), NexCourse® Breast IHC4 (Geneoptix), and the PAM50 Breast Cancer Intrinsic Classifier (ARUP National Reference Laboratory), BreastPRS™ (Signal Genetics) and EndoPredict™ (Sividon Diagnostics). 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.

Oncotype DX, using a slightly different algorithm to calculate results, is also marketed for patients with noninvasive, ductal carcinoma in situ (DCIS) to predict the 10-year risk of local recurrence (DCIS or invasive carcinoma). The stated purpose is to help guide treatment decision making in women with DCIS treated by local excision, with or without adjuvant tamoxifen therapy.

BluePrint® and TargetPrint® Gene expression patterns have led to the identification of molecular subtypes of breast cancer, which have different prognoses and responses to treatment regimens. These molecular subtypes are largely distinguished by the differential expression of estrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor receptor 2 (HER2) in the tumor, and are classified as luminal, basal or HER2 type. Luminal-like breast cancers are ER positive, basal-like breast cancers correlate best with ER, PR and HER2 negative (“triple negative”), and HER2 type with high expression of HER2.

At present, the methodology for molecular subtyping is not standardized, and breast cancer subtyping is routinely assessed by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH).

BluePrint® is an 80-gene expression assay which classifies breast cancer into basal type, luminal type or ERBB2-type. The test is marketed as an additional stratification into a molecular subtype following risk assessment with MammaPrint.

TargetPrint® is a microarray-based gene expression test which offers a quantitative assessment of ER, PR and HER2 overexpression in breast cancer. The test is marketed to be used in conjunction with Mammaprint and BluePrint.

**Regulatory Status**
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 U.S. Food and Drug Administration (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.
POLICY
A. The use of the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (i.e., Oncotype DX) to determine recurrence risk for deciding whether or not to undergo adjuvant chemotherapy may be considered **medically necessary** in women with primary breast cancer meeting the following characteristics:

1. unilateral, non-fixed tumor;
2. hormone receptor positive (that is, estrogen-receptor [ER]-positive or progesterone receptor [PR]-positive);
3. human epidermal growth factor receptor 2 (HER2) negative;
4. tumor size 0.6–1 cm with moderate/poor differentiation or unfavorable features OR tumor size >1cm;
5. node negative (lymph nodes with micrometastases (less than 2 mm in size) are considered node negative for this policy statement);
6. who will be treated with adjuvant endocrine therapy, e.g., tamoxifen or aromatase inhibitors;
7. when the test result will aid the patient in making the decision regarding chemotherapy (i.e., when chemotherapy is a therapeutic option); AND
8. when ordered within 6 months following diagnosis, since the value of the test for making decisions regarding delayed chemotherapy is unknown.

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

C. 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.

D. The use of gene expression assays in men with breast cancer is considered **medically necessary**.

E. All other indications for the 21-gene RT-PCR assay (i.e., Oncotype DX), including determination of recurrence risk in breast cancer patients with positive lymph nodes or patient with bilateral disease, are considered **experimental / investigational**.
F. 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 (i.e., Oncotype DX DCIS) to inform treatment planning following excisional surgery is considered experimental / investigational.

G. The use of other gene expression assays (e.g., MammaPrint, Mammostrat Breast Cancer Test, the Breast Cancer Index, the BreastOncPx, NexCourse Breast IHC4, or PAM50 Breast Cancer Intrinsic Classifier, Breast PRS and EndoPredict) for any indication is considered experimental / investigational.

H. The use of gene expression assays to molecularly subclassify breast cancer (e.g., BluePrint) is considered experimental / investigational.

I. The use of gene expression assays for quantitative assessment of ER, PR and HER2 overexpression (e.g., TargetPrint) is considered experimental / investigational.

Policy Guidelines

1. Unfavorable features that may prompt testing in tumors from 0.3 to 1 cm in size include the following: angiolymphatic invasion, high histologic grade, or high nuclear grade.

2. The 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) 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.

3. According to the American Society of Clinical Oncology-College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer, “a positive HER2 result is IHC [immunohistochemistry] staining of 3+ (uniform, intense membrane staining of >30% of invasive tumor cells), a fluorescent in situ hybridization (FISH) result of more than six HER2 gene copies per nucleus or a FISH ratio (HER2 gene signals to chromosome 17 signals) of more than 2.2; a negative result is an IHC staining of 0 or 1+, a FISH result of less than 4.0 HER2 gene copies per nucleus, or FISH ratio of less than 1.8. Equivocal results require additional action for final determination.” (1)

RATIONALE

In 2005, a TEC Assessment (2) 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 (3) 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 invasive 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 invasive breast cancer patients for the same indications as in the 2005 and 2008 Assessments. (4) The 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.

**Oncotype DX™**

The initial indications for the 21-gene expression profile (Oncotype DX) were newly diagnosed invasive 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 from lymph node-negative disease.

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. (5) 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, (6) multifocal tumors were excluded.

**Lymph Node-negative Patients**

Studies delineating the association between the 21-gene RS and recurrence risk are shown in Table 1. (7-10) Results indicate strong, independent associations between the RS and distant disease recurrence or death from breast cancer. (8, 10) In secondary reclassification analyses of the Paik et al. data, (7, 9) 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. (6)

**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) invasive 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. (4)

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 invasive 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. (11) 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 survival (DFS) or overall survival (OS) in women with early, HER2-negative breast cancer, (12) and therefore may not be prescribed in this population.

- Lymph nodes with micrometastases are not considered positive for purposes of treatment recommendations. (13) 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 estrogen-receptor (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 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. (14, 15)

Several papers related to the use of Oncotype DX have been published since the 2008 Assessment. Some of these papers will be briefly mentioned. Toi et al. confirmed the clinical validity of Oncotype DX in a Japanese population of ER-positive, lymph node-negative patients. (16) Tang et al. compared the prognostic and predictive utility of RS and Adjuvant! in the NSABP B-14 and B-20 trial patients. (17) 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 2 National Surgical Adjuvant Breast and Bowel Project (NSABP) trials, (18) reporting that 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 Oncotype DX using mailed survey and chart review. (19) 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. (20-27) In general, these studies report that comparing recommendations made prior to and revised after knowledge of RS results show that decisions change in about 25-40% of patients, most often from endocrine therapy plus chemotherapy to endocrine therapy alone. For example, in a retrospective reclassification analysis, Joh et al. found that inclusion of the Oncotype DX recurrence scores resulted in a 24.9% change in (after the fact) treatment recommendations, resulting in fewer patients projected to receive chemotherapy. (27) Hassett et al. evaluated registry data from the National Comprehensive Cancer Network (NCCN) Breast Cancer Outcomes Database Project focusing on women diagnosed for hormone-receptor (HR)-positive stage I to III unilateral breast cancer during 2006-2008. Compared to women with Oncotype DX-determined intermediate-risk cancer, women with Oncotype-determined high-risk cancers were more likely to receive chemotherapy (odds ratio [OR]: 12.0; 95% CI: 6.7 to 21.3) and women with low-risk cancers were less likely to receive chemotherapy (OR: 0.1; 95% CI: 0.1 to 0.2). (26) Some view these as evidence of clinical utility because more patients avoid the toxicity of chemotherapy (28); however, there are no actual patient outcomes attached to these studies. 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. (20)
**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. (29) 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 (30, 31); no published studies were found that changed these conclusions.

### Table 1. Summary of Oncotype DX RS and recurrence risk studies.

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Total N</th>
<th>Study Objective</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paik et al. 2004a (7) TAM arm of NSABP B-14 RCT</td>
<td>668</td>
<td>Predict recurrence</td>
<td>RS risk</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Low (&lt;18) Intermediate (18-30) High (&gt;31)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>K-M distant recurrence at 10 yr, % (95% CI)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>All</td>
</tr>
<tr>
<td>Paik et al. 2004b (8)</td>
<td>668</td>
<td>Reclassification study; determine incremental risk compared to conventional classifier.</td>
<td>Risk classification by NCCN¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low (8%) Intermediate High</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>High (92%) Intermediate High</td>
</tr>
<tr>
<td>Bryant 2005 (9) Additional analysis of Paik et al. 2004a data</td>
<td>668</td>
<td>Reclassification study; determine incremental risk compared to conventional classifier</td>
<td>Risk 10-yr classification by Adjuvant Online¹</td>
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<td></td>
<td></td>
<td></td>
<td>Low Int-High</td>
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<tr>
<td></td>
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<td></td>
<td>Int-High (47%)</td>
</tr>
<tr>
<td>Hable et al. 2006 (10) Case control</td>
<td>255 ER+ TAM+; 361 ER+TAM-</td>
<td>Predict mortality</td>
<td>RS risk</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>ER+, TAM-treated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low (&lt;18) Intermediate (18-30) High (&gt;31)</td>
</tr>
</tbody>
</table>

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.¹Percentages are percent of total N.²Estimated 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.
**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. (32) 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. (11) 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 1 cm in size. (33) Patients were randomly assigned to doxorubicin plus cyclophosphamide or docetaxel plus 5 years of endocrine therapy; 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%), 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.”

A previous study by Chang et al. 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). (34) 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). (30) 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 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. (35) However, only medical oncologists who were already using the assay (16% response rate) were surveyed.
thus biasing the results. Finally, no outcomes were reported, providing no firm evidence of clinical utility.

Additional studies are necessary before it is possible to confidently withhold currently recommended chemotherapy (13) from lymph node-positive invasive breast cancer patients with low/intermediate RS results. The RxPONDER (Rx for Positive Node, Endocrine Responsive Breast Cancer) trial, led by the Southwest Oncology Group, will enroll 4,000 women with RS <25 who have early-stage, hormone receptor-positive, HER2-negative breast cancer involving 1 to 3 lymph nodes. Patients will be randomized to receive either chemotherapy with endocrine therapy or endocrine therapy alone. The primary trial outcomes are expected to be completed in December 2016 (available online at: http://clinicaltrials.gov/ct2/show/NCT01272037).

**Patients with DCIS**

Ductal carcinoma in situ (DCIS) is breast cancer located in the lining of the milk ducts that has not yet invaded nearby tissues. It may progress to invasive cancer if untreated. The frequency of DCIS diagnosis in the U.S. has increased in tandem with the widespread use of screening mammography, accounting for about 20% of all newly diagnosed invasive plus noninvasive breast tumors. Recommended treatment is lumpectomy (mastectomy is also an option) with or without radiation treatment; post-surgical tamoxifen treatment is recommended for ER-positive DCIS, especially if excision alone is used. Because the overall rate of ipsilateral tumor recurrence (DCIS or invasive carcinoma) is about 25% at 10 years, it is believed many women are overtreated with radiation therapy. Thus, accurate prediction of recurrence risk may identify those women who may safely avoid radiation.

The Oncotype DX DCIS test uses information from 12 of the 21 genes assayed in the standard Oncotype DX test for early breast cancer. According to the Oncotype website, analyses from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 study (8, 18) and the Habel et al. case-control study (10) were used to select genes that predict the risk of recurrence independent of tamoxifen treatment and ER status. In a retrospective analysis of data and samples from patients in the prospective Eastern Cooperative Oncology Group E5194 study, the Oncotype DX Score for DCIS was compared with the 10-year recurrence risk in a subset of DCIS patients treated only with surgery and some with tamoxifen (n=327). (36) DCIS Score was significantly associated with recurrence outcomes (HR: 2.31; 95% CI: 1.15, 4.49; p=0.02) whether or not patients were treated with tamoxifen. The standard Oncotype DX Score for early breast cancer was not associated with DCIS recurrence outcomes. These studies address the development of the Oncotype DX DCIS Score and the clinical validity (association of the test result with recurrence outcomes). Whether women are better categorized as to their recurrence risk by the Oncotype DX DCIS Score compared with standard clinical indicators of risk has not yet been addressed.

**MammaPrint®**

MammaPrint, also called the 70-gene signature, is a prognostic test for women with ER-positive or ER-negative, lymph node-negative invasive breast cancer. The 2008 TEC Assessment (3) reviewed available studies (37-41) 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. (37)

Studies of primarily node-negative disease

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. (42) 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. An additional small study of samples from women with lymph node-negative disease suggested that the 70-gene signature was an independent and significant predictor of distant metastases, but the small number of events limited conclusions. (43)

Original validation studies included patients with both node-negative and node-positive disease. Mook et al. retrospectively evaluated 148 consecutive, node-negative, post-menopausal patients, with primarily ER-positive tumors; only 18% received 2 years of adjuvant tamoxifen and none chemotherapy. (44) 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% (CI: 60-84%). The authors reported on concordance with Adjuvant! Online, but did not conduct a net reclassification analysis to determine additional impact of the MammaPrint signature on outcomes.

The Microarray Prognostics in Breast Cancer (RASTER) study, published in 2013, was designed to assess feasibility of implementation and impact on treatment decisions of the MammaPrint 70-gene signature, as well as recurrence outcomes. (45) The study followed 427 node-negative, early-stage breast cancer patients who participated in the RASTER Study and had a 70-gene signature (MammaPrint), which was available to help direct post-surgery treatment decisions, and which was compared to Adjuvant! Online. All of the patients were aged 18-61 years old and had a histologically-confirmed unilateral, unifocal, primary operable, invasive adenocarcinoma of the breast. Median follow-up was 61.6 months. Eighty percent of patients were ER positive. Discordant risk estimates between Mammaprint and AOL occurred in 38% of the cases (161/427). Most discordant cases were Mammaprint low-risk and AOL high-risk (124/427= 29%), whereas 37 cases (37/427 =9%) had a high-risk Mammaprint and a low-risk AOL estimation. Use of Mammaprint reduced the proportion of high-risk patients as classified by AOL by 20% (87/427). The 5-year distant recurrence-free interval (DRFI) probabilities were excellent for patients who were clinically high-risk but had a low-risk score with Mammaprint, even in the absence of adjuvant systemic therapy. The results of patients receiving adjuvant therapy are presented in Table 2. The results suggest that MammaPrint is a better prognostic classifier than standard clinical and pathological classifiers. However, limitations of the study are several. The patient numbers are low and event numbers very low, making firm conclusions difficult. The actual treatment decisions that were made were based on restrictive Dutch guidelines from 2004 and patient’s and doctor’s preferences. Additionally, the adjuvant online risk estimates were based on 10- year outcomes, whereas the RASTER outcomes were at 5 years. Since most clinical relapses in lymph node negative, ER positive breast cancers do not occur until 5 or even 10 years.
after diagnosis, with or without the use of adjuvant therapy, the study data should be considered not yet mature.

Table 2. Results of the RASTER study, showing 5-year DDFS differences of a 70-gene signature - Low classification vs. low and high Adjuvant Online! Classification

<table>
<thead>
<tr>
<th>70-gene signature category</th>
<th>Adjuvant Online! Category</th>
<th>AST</th>
<th>5-year DRFI (%), 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Low</td>
<td>7/95 7%</td>
<td>95.3 (90.9-100)</td>
</tr>
<tr>
<td>High</td>
<td>Low</td>
<td>32/37 86%</td>
<td>100 (100-100)</td>
</tr>
<tr>
<td>Low</td>
<td>High</td>
<td>54/124 44%</td>
<td>98.4 (96.1-100)</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
<td>166/171 (97%)</td>
<td>89.8 (85.1-94.8)</td>
</tr>
</tbody>
</table>

AST- adjuvant systemic therapy; DRFI, distant recurrence-free interval

Studies of mixed or node-positive disease

In a study of node-positive disease, Mook et al. evaluated 241 patients with 1-3 positive nodes and primarily ER-positive, HER2-negative tumors treated variably. (46) The 70-gene signature was a significant predictor of outcome. Reclassification analysis using Adjuvant! Online vs. MammaPrint 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, (19) 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. Pilot phase results of the MINDACT trial were published in 2011 and showed successful implementation of the biomarker-stratified trial design and compliance with chemotherapy treatment according to the risk of recurrence according to MammaPrint. (47)

The 2012 I-SPY trial evaluated 237 patients with locally advanced disease (node-positive) by correlating imaging and MammaPrint signatures with outcomes of pathologic complete response (pCR) and recurrence-free survival (RFS). (48) Despite having locally advanced disease, patients with 70-gene low-risk profiles tended not to respond to chemotherapy and to have good short-term RFS. Results are shown in Table 3.

Table 3. Results of I-SPY 1: MammaPrint 70-gene signature results and trial outcomes

<table>
<thead>
<tr>
<th>MammaPrint Risk Category</th>
<th>Pathological complete response (pCR)</th>
<th>Recurrence-free survival (RFS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate of pCR, % (n/N)</td>
<td>Odds ratio (p value)</td>
</tr>
<tr>
<td>Low 11 (9)</td>
<td>0% (0/11)</td>
<td>0.00</td>
</tr>
<tr>
<td>High 109 (91)</td>
<td>24% (25/105)</td>
<td>(0.02)</td>
</tr>
</tbody>
</table>

*denotes significant proportional hazard ratio (likelihood ratio p<0.05). A value of 0.00 indicates that there were no recurrences in this category among patients who had a pCR.

Other studies 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 (<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. (49) 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 2.7 (95% CI: 1.88–3.88, p<0.001). Results are confounded by nodal status, HER2 status, and adjuvant therapy.

Kunz conducted a pooled re-analysis of a subgroup of patients aged 35-55 years from previously published studies. (50) 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 distant metastasis-free survival was 88% (95% CI: 84-92%). Bighin et al. reported difficulties in that nearly 25% of samples from 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. (51)

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. (52) 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.

**Ongoing trials**
MINDACT trial (Microarray In Node-negative and 1-3 Node-Positive Disease May Avoid ChemoTherapy) is a prospective randomized trial comparing Mammaprint with Adjuvant! Online for decision making about adjuvant chemotherapy.

**Summary**
The majority of MammaPrint studies, including the early validation studies, suffered from confounding in heterogeneous sample populations. Subsequent pooled re-analyses of subpopulations controlled for one variable (e.g., nodal status), but confounding remained 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. The recently published RASTER (Microarray Prognostics in Breast Cancer) study represents an improved study design, and results suggest that MammaPrint may accurately re-classify early, node-negative breast cancer patients classified high risk for recurrence by clinical and pathologic variables to low risk, such that chemotherapy may not be necessary. However, patient numbers and events are too low for firm conclusions, and follow-up is not yet sufficiently mature.

**BluePrint™ and TargetPrint®**
The BluePrint molecular subtyping profile was developed using 200 breast cancer specimens that had concordant ER, PR and HER2 protein levels by immunohistochemistry and TargetPrint mRNA readout. (53) Using a threefold cross validation procedure, the 80 genes thought to best discriminate the three molecular subtypes were identified. BluePrint was confirmed on 4 independent validation cohorts (n=784), which included patients from a consecutive series of patients seen at Netherlands Cancer Institute and treated with adjuvant tamoxifen monotherapy (n=274), a group of patients from the RASTER trial (n=100), and two publicly available data sets (n=410). In addition, in 133 patients treated with neoadjuvant chemotherapy, the molecular
subtyping profile was tested as a predictor of chemotherapy response. The authors conclude that use of BluePrint classification showed improved distribution of pathologic complete response (pCR) among molecular subgroups compared with local pathology: 56% of the patients had a pCR in the basal-type subgroup, 3% in the MammaPrint low-risk, luminal-type subgroup, 11% in the MammaPrint high-risk, luminal-type subgroup, and 50% in the HER2-type subgroup.

Nguyen and colleagues undertook a comparison of molecular subtyping with BluePrint, MammaPrint and TargetPrint to locally assessed clinical subtyping using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). The three gene expression assays were performed on fresh tumor tissue at Agendia Laboratories, blinded for pathologic and clinical data. IHC and FISH testing were performed according to local practice at 11 institutions in the U.S. and Europe. ER, PR and HER2 were performed on 132 samples. The concordance between BluePrint and IHC and FISH testing was 94% for both the basal-type and luminal-type subgroups, and 95% for the HER2-type. Concordance of BluePrint with subtyping using TargetPrint was 98% for the basal-type, 96% for the luminal-type, and 97% for the HER2-type.

**Breast Cancer Index SM**

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 foregoing 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.

Jankowitz et al. evaluated tumor samples from 265 ER-positive, lymph node (LN)-negative, tamoxifen-treated patients from a single academic institution’s cancer research registry. BCI categorized 55%, 21%, and 24% of patients as low, intermediate and high risk, respectively, for distant recurrence. The 10-year rates of distant recurrence were 6.6% (95% CI: 2.3-10.9%),
12.1% (95% CI: 2.7-21.5%), and 31.9% (95% CI: 19.9-43.9) and of breast cancer-specific mortality were 3.8%, 3.6% and 22.1% in low-, intermediate-, and high-risk groups, respectively. In a multivariate analysis, BCI was a significant predictor of distant recurrence and breast cancer-specific mortality. In a time-dependent (10-year) ROC curve analysis of recurrence risk, the addition of BCI to Adjuvant! Online risk prediction increased maximum predictive accuracy in all patients from 66% to 76% and in tamoxifen-only treated patients from 65% to 81%. (62)

**Mammostrat™ Breast Cancer Test**

Mammostrat is an immunohistochemistry (IHC) test intended to evaluate risk of breast cancer recurrence in postmenopausal, node-negative, ER-positive invasive 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). (63) In a validation study in an independent cohort, a multivariable model predicted 50%, 70%, and 87% 5-year DFS for patients classified as high, moderate, and low prognostic risk, respectively, by the test results (p=0.0008). (63) 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. (64) 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. (65) 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.
BreastOncPx™

The BreastOncPx test is a reverse transcriptase-polymerase chain reaction (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 (66); 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. (66) 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.

NexCourse Breast IHC4

NexCourse Breast IHC4 evaluates the protein expression of ER/PR, HER2, and Ki-67 to provide a combined recurrence risk score. The assay technology uses quantitative image analysis to measure immunofluorescent signals, with results that can be combined in an algorithm to generate the recurrence risk score. The use of quantitative immunofluorescence is said to increase sensitivity, be more reproducible, and allow specific measurement of tumor cells. (67, 68)

Cuzick et al. evaluated 1,125 ER-positive patients from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial who did not receive adjuvant chemotherapy, already had the Oncotype DX Recurrence Score (RS) computed, and had adequate tissue for the IHC4 measurements. (69) Of these, 793 were node-negative and 59 were HER2-positive (but were not treated with trastuzumab). A prognostic model that combined the 4 immunohistochemical markers was
created (IHC4). In a model combining either IHC4 or Oncotype DX Rs with classical prognostic variables, the IHC4 score was found to be similar to the Oncotype DX RS, and little additional prognostic value was seen in the combined use of both scores. In a direct comparison the IHC4 score was modestly correlated with the Oncotype DX RS ($r=0.72$); the correlation was similar for node-negative patients ($r=0.68$). As an example, for a 1-2 cm, node-negative poorly differentiated tumor treated with anastrozole, 9-year distant recurrence at the 25th versus 75th percentiles for IHC4 and Oncotype DX were 7.6% versus 13.9% and 9.2% versus 13.4%, respectively. The IHC4 score was validated in a separate cohort of 786 ER-positive women, about half of whom received no endocrine treatment. The IHC4 score was significant for recurrence outcomes (HR: 4.1; 95% CI: 2.5-6.8).

Barton et al. assessed the clinical utility of IHC4 plus clinicopathologic factors (IHC4 + C) by comparison with Adjuvant! Online and the Nottingham Prognostic Index (NPI). (70) The study prospectively gathered clinicopathologic data for consecutively treated postmenopausal patients ($n=101$ evaluable) with hormone receptor-positive, HER2-negative, LN-negative or -positive with 1-2 nodes, resected early breast cancer. Of 59 patients classified as intermediate-risk group by the NPI, IHC4 reclassified 24 to low risk and 13 to high risk. IHC4 reclassified 13 of 32 Adjuvant! high-risk patients to intermediate risk, and 3 of 32 to low risk. In addition, 15 of 26 Adjuvant! intermediate-risk patients were reclassified to low risk. No Adjuvant! low-risk patients were reclassified high risk.

**PAM50 Breast Cancer Intrinsic Classifier**

The initial development of the PAM50 breast cancer Intrinsic Classifier was reported by Parker et al. (71) 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 3 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. (72) 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.

Cheang et al. determined PAM50 intrinsic subtypes for samples from a clinical trial randomizing premenopausal women with node-positive breast cancer to 2 different regimens of chemotherapy. The PAM50 intrinsic subtype for 476 tumors was correlated to relapse-free
survival (RFS; p=0.0005) and overall survival (OS; p<0.0001). The HER2-enriched subgroup (22%) showed the greatest benefit from cyclophosphamide-epirubicin-fluorouracil (CEF) versus cyclophosphamide-methotrexate-fluorouracil (CMF), with absolute 5-year RFS and OS differences exceeding 20%. There was a less than 2% difference for non-HER2-enriched tumors (interaction test p=0.03 for RFS and 0.03 for OS). Within clinically defined HER2-positive tumors, 79% (72 of 91) were classified as the HER2-enriched subtype by gene expression, and this subset was associated with better response to CEF versus CMF (62% vs. 22%, p=0.0006). There was no significant difference in benefit from CEF versus CMF in basal-like tumors. (73)

**BreastPRS**

BreastPRS is a gene expression assay that analyzes 200 genes in its algorithm, and was validated from a meta-analysis of publically available genomic datasets. (74) BreastPRS is a binary assay which stratifies patients into low- and high-risk groups. (75)

D’Alfonso et al. sought to translate a previously published validation study of BreastPRS, using fresh-frozen tissue, to formalin-fixed paraffin-embedded (FFPE) tumor samples. The authors compared the BreastPRS prognostic index to the OncotypeDX assay and correlated recurrence scores with clinicopathologic features, and used publically available whole genome profiles from a series of untreated ER+ node negative patients to investigate the ability of BreastPRS to reclassify OncotypeDX intermediate-risk patients into high- versus low-risk categories with clinically significant differences in outcome. (75) A linear relationship of the BreastPRS prognostic score was observed between fresh-frozen and FFPE formats. BreastPRS recurrence scores were compared with OncotypeDX recurrence scores from 246 patients with invasive breast carcinoma and known Oncotype DX results. Using this series, a 120-gene Oncotype DX approximation algorithm to predict Oncotype DX risk groups was then applied to a series of untreated, ER-positive, node-negative patients from previously published studies with known clinical outcomes. Of the 30 high-risk Oncotype DX cases, 27 (90%) were classified as high-risk by BreastPRS, and 95 low-risk Oncotype DX cases (76%) were classified as low-risk by BreastPRS. The correlation of recurrence score and risk group between Oncotype DX and BreastPRS was statistically significant (p<0.0001). Fifty-nine of 260 (23%) patients from four previously published studies were classified as intermediate-risk when the 120-gene Oncotype DX approximation algorithm was applied. BreastPRS reclassified the 59 patients into binary risk groups (high- vs. low-risk), with 23 (39%) patients classified as low-risk and 36 (61%) as high-risk (p=0.029, HR: 3.64, 95% CI: 1.40-9.50). At 10 years from diagnosis, the low-risk group had a 90% recurrence-free survival (RFS) rate compared to 60% for the high-risk group. The authors concluded that the BreastPRS recurrence score is comparable with OncotypeDX and can reclassify Oncotype DX intermediate-risk patients into two groups with significant differences in RFS. (75)

**EndoPredict**

Varga et al. analyzed the Endopredict (EP) test in 34 hormone positive, invasive breast cancer cases and compared the EP scores with the Oncotype DX Recurrence-scores (RS) obtained from the same cancer samples. (76) EP classified 11 patients as low-risk and 23 patients as high-risk, whereas the RS Score defined 15 patients as low-risk, 10 patients as intermediate-risk in and 9 patients as high-risk. There were major discrepancies in 6 of 34 cases (18%), with low-risk RS classified as high-risk by EP in 6 cases. When the RS intermediate and high-risk groups were combined, the concordance between both tests was 76%. The clinical relevance of these discrepant test results with respect to outcome is unknown.
Test Comparison Studies

Dowsett et al. compared the risk of recurrence (ROR) score generated by PAM50 to the OncotypeDx 21-gene recurrence score (RS), four immunohistochemical markers (IHC4) for ER, PR, Ki67 and HER2, and a clinical treatment score (CTS). Patients had ER-positive, primary breast disease treated with anastrozole or tamoxifen in the ATAC trial (a double-blinded, phase 3 clinical trial that was designed to compare the ability of anastrozole, tamoxifen, and the two drugs in combination to prevent breast cancer recurrence in postmenopausal women with hormone receptor-positive tumors). Lymph node-negative and positive patients were included. mRNA from 1,017 patients was assessed for ROR, and likelihood ratio (LR) tests and concordance indices were used to assess the prognostic information provided beyond that of a CTS, RS, ROR or IHC4. The CTS integrated prognostic information from nodal status, tumor size, histopathologic grade, age and anastrozole or tamoxifen treatment. The authors concluded that the ROR added significant prognostic information beyond CTS in all patients (p<.001), and in all 4 subgroups: lymph node negative, lymph node positive, HER2 negative and HER2 negative/node-negative, and that more information was added by ROR than RS. More patients scored as high risk of recurrence and fewer as intermediate risk by ROR than RS.

Hornberger performed a systematic review of the literature on the clinical validity/utility, change in clinical practice, and economic implications of early-stage breast cancer stratifiers. Fifty-six articles published original evidence addressing the 21-gene recurrence score [OncotypeDX] (n = 31), 70-gene signature [Mammaprint] (n = 14), Adjuvant! Online (n = 12), 5-antibody immunohistochemistry panel [Mammostrat] (n = 3), and 14-gene signature [BreastOncPx] (n = 1). The results of the review found that OncotypeDx recurrence score satisfied level I evidence for estimating distant recurrence risk (DRR), OS, and response to adjuvant chemotherapy, and level II evidence for estimating local recurrence risk. Mammostrat and Mammaprint satisfied level II evidence for estimating DRR and OS. Adjuvant! Online satisfied level II evidence for estimating DRR, OS, and chemotherapy response. BreastOncPx satisfied level III evidence for predicting DRR and OS. Ten studies reported changes in clinical practice patterns using the 21-gene recurrence score. Overall, the 21-gene recurrence score was associated with change in treatment recommendations and/or decisions in 20.6-74.0% of cases.

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.

Two recent papers compared the Oncotype DX and other gene expression profiles. Kelly et al.
(80) evaluated Oncotype DX and PAM50 in 108 cases and found good agreement between the 2
assays for high- and low-prognostic risk assignment, but PAM50 assigned about half of Oncotype
DX intermediate-risk patients to the PAM50 luminal A (low risk) category. Prat et al. evaluated
several gene expression tests of interest including Oncotype DX, PAM50 and MammaPrint in 594
cases and found all predictors were significantly correlated (Pearson correlation range: 0.36-0.79;
p<0.0001 for each comparison). (24)

**Additional Applications**

Based on a study published in May 2008 that compared the Oncotype DX ER and PR results to
traditional IHC results, (81) 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 2 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. (1) The HER2 component of the 21-
gene assay has been shown in one large study to strongly correlate with FISH results, (82) but
significant discrepancies have been noted in another. (83) As a result, and without evaluation
and support from guidelines, it has been recommended that the 21-gene assay not be ordered to
determine or confirm HER2. (84)

No published literature on the use of gene expression profiling in men with breast cancer is
identified.

**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 recurrence score (RS) is strongly associated with risk of distant recurrence in women with invasive 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% confidence interval (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 sufficiently large, to recommend avoiding otherwise currently recommended treatment. Additional studies are necessary and ongoing.

For women with ductal carcinoma in situ (DCIS), the use of a subset of genes from the 21-gene recurrence score (i.e., Oncotype DX DCIS) to predict recurrence and inform treatment planning post-excision, development and clinical validity studies have not yet been published to allow full evaluation. Moreover, no information is yet available on whether women are better categorized as to their recurrence risk by the Oncotype DX DCIS Score compared with standard clinical indicators of risk.

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. The recently published Microarray Prognostics in Breast Cancer (RASTER) study represents an improved study design, and results suggest that MammaPrint may accurately re-classify early, node-negative invasive breast cancer patients classified high risk for recurrence by clinical and pathologic variables to low risk, such that chemotherapy may not be necessary. However, patient numbers and events are too low for firm conclusions, and follow-up is not yet sufficiently mature.

BluePrint and TargetPrint The 80-gene expression assay BluePrint discriminates between three breast cancer molecular subtypes and TargetPrint is a method to measure ER, PR and HER2 as an alternative to immunohistochemistry and FISH. The clinical utility of BluePrint is unknown, as it is not clear how this test will add to treatment decision making using currently available, accepted methods (e.g., clinical and pathologic parameters). The incremental benefit of using TargetPrint as an alternative to current standard methods of measuring ER, PR and HER2 has not been demonstrated, nor is it included in recommendations for testing issued by ASCO and CAP.
**Mammostrat Breast Cancer Test, Breast Cancer Index, BreastOncPx, Pam50 Breast Cancer Intrinsic Classifier, NexCourse Breast IHC4.** 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 early, invasive 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 receiver operating characteristic (ROC) analysis comparing the test with Adjuvant!, but no clear evidence supporting clinical utility was available. NexCourse Breast IHC4 (immunohistochemical markers) was compared with standard clinicopathological prognostic classifiers in a reclassification analysis and was shown to accurately reclassify significant numbers of patients from high and intermediate risk to low risk, but numbers in the study were small and insufficient for conclusions.

**Practice Guidelines and Position Statements**

The 2013 National Comprehensive Cancer Network (NCCN) guidelines (v3.2013) (13) indicate that Oncotype DX (termed the “21-gene RT-PCR assay”) is an option (category 2A) in invasive 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 with unfavorable features OR size larger than 1 cm.

The 2007 American Society of Clinical Oncology (ASCO) guidelines (85) 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. (86)

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. (13, 85)

In 2010, ASCO and the College of American Pathologists (CAP) issued recommendations on immunohistochemical testing for ER and PR (87), and issued recommendations in 2007 (1) (updated in 2013) (88) for HER2 testing by immunohistochemical and FISH methods. Recommendations do not address the use of gene expression assays to test for ER, PR or HER2 expression.
CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

S3854 Gene expression profiling panel for use in the management of breast cancer treatments.

There are no specific CPT codes for these laboratory tests. Effective 1/1/06, an S code was designated for this test: S3854.

DIAGNOSIS

174.0 Malignant neoplasm of female breast; Nipple and areola
174.1 Malignant neoplasm of female breast; Central portion
174.2 Malignant neoplasm of female breast; Upper-inner quadrant
174.3 Malignant neoplasm of female breast; Lower-inner quadrant
174.4 Malignant neoplasm of female breast; Upper-outer quadrant
174.5 Malignant neoplasm of female breast; Lower-outer quadrant
174.6 Malignant neoplasm of female breast; Axillary tail
174.8 Malignant neoplasm of female breast; Other specified sites of female breast
175.0 Malignant neoplasm of male breast; Nipple and areola
233.0 Carcinoma in situ of breast

ICD0-10 Diagnosis (Effective October 1, 2014)

C50.011 Malignant neoplasm of nipple and areola, right female breast
C50.012 Malignant neoplasm of nipple and areola, left female breast
C50.021 Malignant neoplasm of nipple and areola, right male breast
C50.022 Malignant neoplasm of nipple and areola, left male breast
C50.111 Malignant neoplasm of central portion of right female breast
C50.112 Malignant neoplasm of central portion of left female breast
C50.211 Malignant neoplasm of upper-inner quadrant of right female breast
C50.212 Malignant neoplasm of upper-inner quadrant of left female breast
C50.311 Malignant neoplasm of lower-inner quadrant of right female breast
C50.312 Malignant neoplasm of lower-inner quadrant of left female breast
C50.411 Malignant neoplasm of upper-outer quadrant of right female breast
C50.412 Malignant neoplasm of upper-outer quadrant of left female breast
C50.511 Malignant neoplasm of lower-outer quadrant of right female breast
C50.512 Malignant neoplasm of lower-outer quadrant of left female breast
C50.611 Malignant neoplasm of axillary tail of right female breast
C50.612 Malignant neoplasm of axillary tail of left female breast
C50.811 Malignant neoplasm of overlapping sites of right female breast
C50.812 Malignant neoplasm of overlapping sites of left female breast
### REVISIONS

**11-09-2011**

In the Policy section:
- Revised the policy language as indicated below to the current language:
  
  "Patient must meet all the following criteria:
  
  A Gene Expression Survey such as Oncotype DX™, is a diagnostic test designed to assist in the decision making in regards to chemotherapy treatments based on the possibility of the recurrence of breast cancer in those women with newly diagnosed, early-stage breast cancer. The cancer diagnosis has all of the following characteristics:
  
  - Estrogen-receptor positive (ER+)
  - Newly diagnosed
  - Node negative
  - Stage I or II (based on size only—over 2 cm)"

In the Policy Guidelines section:
- Added the following:
  
  "According to the American Society of Clinical Oncology-College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer, “a positive HER2 result is IHC [immunohistochemistry] staining of 3+ (uniform, intense membrane staining of >30% of invasive tumor cells), a fluorescent in situ hybridization (FISH) result of more than six HER2 gene copies per nucleus or a FISH ratio (HER2 gene signals to chromosome 17 signals) of more than 2.2; a negative result is an IHC staining of 0 or 1+, a FISH result of less than 4.0 HER2 gene copies per nucleus, or FISH ratio of less than 1.8. Equivocal results require additional action for final determination.” (1)"

Updated the Rationale section.
Updated the Reference section.

**04-12-2013**

Updated Description section.

In Policy section:
- In Item D, revised the following "patients who are lymph node positive" to read "patients with positive lymph nodes".
- In Item D, inserted "or patient with bilateral disease" to read "patients with positive lymph nodes or patient with bilateral disease,"
- Added Item E, "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 (i.e., Oncotype DX DCIS) to inform treatment planning following excisional surgery is considered experimental / investigational."
- In Item F, revised the following "The use of other gene expression assays (e.g., MammaPrint, Mammostrat, or the THEROS Breast Cancer IndexSM) for any indication is considered experimental / investigational." to read "The use of other gene expression assays (e.g., MammaPrint, Mammostrat Breast Cancer Test, the Breast Cancer Index, The BreastOncPx, NexCourse Breast IHC4, or PAM50 Breast Cancer Intrinsic Classifier) for any indication is considered experimental / investigational."

Updated Rationale section.

In Coding section:
- Added diagnosis code, 233.0

Updated Reference section.
03-27-2014 | Updated Description section.
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In Policy section:
- Added new Item D, "The use of gene expression assays in men with breast cancer is considered medically necessary.
- In Item G, added "Breast PRS and EndoPredict" to read "...or PAM50 Breast Cancer Intrinsic Classifier, Breast PRS and EndoPredict) for any indication is considered experimental / investigational."
- Added Item H, "The use of gene expression assays to molecularly subclassify breast cancer (e.g., BluePrint) is considered experimental / investigational."
- Added Item I, "The use of gene expression assays for quantitative assessments of ER, PR, and HER2 overexpression (e.g., TargetPrint) is considered experimental / investigational."

Updated Rationale section.

In Coding section:
- Added ICD-10 Diagnosis (Effective October 1, 2014)

Updated Reference section.

REFERENCES


87. Available online at: http://jco.ascopubs.org/content/28/16/2784.full.


Other References
1. Blue Cross Blue Shield of Kansas Oncology Liaison Committee, February 20, 2007 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report. MAC-01-07).
2. Blue Cross and Blue Shield of Kansas Medical Advisory Committee meeting, April 19, 2007 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report. MAC-01-07).
3. Blue Cross Blue Shield of Kansas Pathology Liaison Committee, May 2010; May 2011.
4. Blue Cross Blue Shield of Kansas Oncology Liaison Committee, CB, May, 2011
5. Blue Cross Blue Shield of Kansas Oncology Liaison Committee, February 2009; February 2013

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