



# CIGNA MEDICAL COVERAGE POLICY

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**Subject Genetic Expression Assays for Breast Cancer Prognosis**

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## Hyperlink to Related Coverage Policies

Circulating Tumor Cells Testing  
 Comparative Genomic Hybridization Testing  
 (Chromosomal Microarray Analysis)  
 Pharmacogenetic Testing  
 Tumor Markers for Diagnosis and  
 Management of Cancer

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## Coverage Policy

**CIGNA covers Oncotype DX™ Breast Cancer Assay as medically necessary to assess the need for adjuvant chemotherapy in women with recently diagnosed breast cancer when ALL of the following criteria are met:**

- Breast tumor is stage 1 or stage 2.
- The individual is axillary-node negative or has axillary-node micrometastasis no greater than 2.0 millimeters.
- There is no evidence of distant metastatic breast cancer.
- Breast tumor is estrogen-receptor positive.
- Breast tumor is HER2-receptor negative.
- The individual is a candidate for possible adjuvant chemotherapy (i.e., chemotherapy is not precluded due to other factors), and testing is being done specifically to guide the decision as to whether or not adjuvant chemotherapy will be used.

**CIGNA does not cover Oncotype DX for any other clinical evaluation or any other assays of genetic expression in tumor tissue (e.g., Breast Cancer Gene Expression Ratio, HERmark® Breast Cancer Assay, MammaPrint®, Rotterdam Signature 76-Panel) because they are considered experimental, investigational or unproven.**

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## General Background

Breast cancer is a malignant tumor that originates in the breast cells. If the patient is suspect for breast cancer, needle aspiration and/or a biopsy may be performed. Tissue obtained from a biopsy may be tested by a hormone receptor assay to determine the presence or absence of estrogen (i.e., estrogen-receptive- [ER] positive or ER-negative) and progesterone (i.e., progesterone [PR]-positive or PR-negative), and for the presence of the human epidermal growth factor receptor 2 [HER2], also called HER2/neu, epidermal growth factor receptor 2 (EGFR2), and erbB2. Breast tumors are also staged according to tumor size (T), lymph node involvement (N) and metastasis (M).

Men can also acquire breast cancer. The pathology is similar to females. Prognostics factors in men include the size of the tumor and lymph node involvement. ACS and NCI recommend testing for estrogen- and progesterone-receptor status in men. A small number of breast cancers in men may express the HER2/neu protein (American Cancer Society [ACS], 2010; National Cancer Institute [NCI], 2010).

Currently, clinicopathologic and immunohistochemistry markers and algorithm tools are used to assist the physicians in predicting the 10-year disease-free and overall survival of patients based upon prognostic factors. These predictions are taken into consideration during the management of breast cancer patients in order to offer the optimal treatment pathways, including the use chemotherapy. However, considerable differences exist regarding the selection of women who should be treated with adjuvant chemotherapy. It is suspected that patients with ER-positive, lymph node negative (LNN) breast cancer receive chemotherapy without clear benefit, leading to potential over-treatment, while others destined to experience recurrence are not treated. Better prognostic tools are needed to help determine optimal treatment options for patients with early-stage breast cancer (Andre and Pusztai, 2006; Bogaerts, et al., 2006; Kaklamani, 2006; Lyman and Kuderer, 2006).

Assays of genetic expression, gene expression analysis, or gene-expression profiling has been proposed as an adjuvant tool to assist in determining overall survival, recurrence probability, appropriate treatment options, and responsiveness to chemotherapy. Used in conjunction with consensus guidelines and risk assessments, gene profiling assays may help to identify those women who do not need adjuvant chemotherapy (National Comprehensive Cancer Network<sup>®</sup>, 2010, [NCCN<sup>®</sup>], 2009; ECRI, 2008; Paik, 2006).

The four major platforms utilized for gene profiling include immunohistochemistry (IHC), fluorescent in situ hybridization (FISH), polymerase chain reaction (PCR), and microarray assays. IHC involves designing monoclonal antibodies that bind to the molecule being assessed. Formalin-fixed paraffin-embedded tissue is then stained with the antibodies and the expression of the protein is assessed under a microscope. FISH is an established technique that labels specific regions of deoxyribonucleic acid (DNA), using sequence specific oligonucleotides (i.e., short sequences of DNA) to identify chromosomal deletions, additions or rearrangements. Because FISH uses individual probes, it reveals DNA aberrations of only the probe-targeted segments. PCR is an established laboratory method used to make numerous copies of a specific DNA sequence, utilizing pairs of oligonucleotide primers to replicate and alternate rounds of DNA. Real-time polymerase chain reaction, also called quantitative real time polymerase chain reaction (Q-PCR/qPCR/qrt-PCR) or kinetic polymerase chain reaction (KPCR), is a PCR technology used to simultaneously amplify and quantify the targeted DNA molecule. In reverse transcriptase PCR (RT-PCR) an RNA strand is reverse transcribed into its DNA complement (cDNA). According to NACB (2008), a microarray assay "is a compact device that contains a large number of well-defined immobilized capture molecules (e.g. synthetic oligos, PCR products, proteins, antibodies) assembled in an addressable format". DNA biochips are the best-known type of microarrays and are miniature arrays of oligonucleotides attached to a glass or plastic surface. The chips allow examination of gene activity (expression profiling) and identify gene mutations or single nucleotide polymorphisms (SNPs) (American Association of Clinical Chemistry [AACC], 2010; NCCN, 2010; Turaga, et al., 2010; National Academy of Clinical Biochemistry [NACB], 2009; NACB 2008; Kibel and Reiter, 2007).

Utilization of the four platforms has allowed development of various genetic expression assays for breast cancer. The Oncotype DX<sup>™</sup> 21-gene breast cancer assay (Genomic Health, Redwood City, CA) has been widely accepted and is recommended by the American Society of Clinical Oncologist (ASCO) (2007) and NCCN (2010) for use in a specific subgroup of women with breast cancer. The MammaPrint<sup>®</sup> 70-gene assay (Molecular Profiling Institute [MPI] Inc., Phoenix, AZ; and Agendia BV, Amsterdam, The Netherlands) has received FDA

approval. Numerous other assays such as the Breast Cancer Gene Expression Ratio (i.e., H/I™) (AviaraDx, Inc., Carlsbad, CA), HERmark Breast Cancer Assay (Monogram Biosciences, South San Francisco, CA) and the Rotterdam Signature 76-gene panel (Veridex LLC, a Johnson & Johnson Co, Warren, NJ) have also been proposed for use. Some assays are performed in a centralized Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory which means the test does not require FDA approval. Various companies are seeking FDA approval for assays, which allows distribution and use by multiple laboratories. These assays are not advocated as stand-alone tools. They are recommended as an adjuvant tool to be used with other recognized prognostic indicators.

### **Oncotype DX Breast Cancer Assay**

The purpose of Oncotype DX Breast Cancer Assay is to quantify the likelihood of distant recurrence in a woman with breast cancer, and is used as one factor in determining whether or not a patient is a candidate for chemotherapy. The test is recommended to be conducted after the original breast cancer surgery. Using tumor tissue, RNA is extracted, purified and analyzed for expression of a panel of 21 genes using quantitative reverse transcription polymerase chain reaction (RT-PCR) on formalin-fixed, paraffin-embedded tumor tissue. A Recurrence Score™ (RS) is calculated from the gene expression results using a proprietary Oncotype DX algorithm. The RS is based on a scale of 0–100. A score of less than 18 is considered low-risk; a score between 18 and 31 is intermediate-risk; and a score over 31 is high-risk. Each RS correlates with a specific likelihood of distant recurrence at 10 years. This assay is not proposed for or used as a test to monitor the response of a specific chemotherapy drug.

**Literature Review:** The published peer-reviewed literature supports the accuracy and clinical utility of Oncotype in its ability to predict the benefits of chemotherapy in women with localized stage 1 or stage 2 breast cancer who are ER-positive, HER2-receptor negative with no evidence of metastasis. The patient should also be axillary-node negative which includes micrometastasis no greater than 2.0 millimeters. Tissue samples from tumor banks were used to validate the prognostic ability of the 21-gene assay. Studies reported that patients with a low recurrence score (RS) had a 10-year distant recurrence-free survival rate of 93.2%, 85.7% for patients with an intermediate RS, and 69.5% for patients with a high RS (NCCN, 2010; Toi, et al., 2010; Habel, et al., 2006; Paik, et al., Aug 2006; Cobleigh, et al., 2005; Paid, et al., 2004). Supporting data on the use of Oncotype in men and the value of repeat assays after the initial assessment are lacking.

Most recently Genomics has expanded the criteria for Oncotype to include postmenopausal women, hormone-receptor positive, with node positive (1–3 nodes) breast cancer. The prognostic value of this assay is also being studied in women with loco regional recurrence and disease free survival at five-years. However, the evidence in the peer-reviewed literature does not support clinical utility and improved health outcomes of Oncotype in these subsets of breast cancer patients.

Dowsett et al. (2010) evaluated 1231 tissue samples from a previously reported randomized controlled trial to determine the prognostic value of Oncotype for distant recurrence in hormone receptor-positive postmenopausal women with localized node-negative (NO) (n=872) or node-positive (N+) (n=306) breast cancer patients who were treated with either tamoxifen (n=609) or anastrozole (n=622). The samples were obtained from the tamoxifen and anastrozole arms of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trial (n=4160) which evaluated the safety and efficacy of five years of anastrozole, tamoxifen, or both in postmenopausal women. Sixty-three patients had  $\geq 4+$  nodes and 243 patients had 1–3 positive nodes (node status was unknown in the remaining patients). Tumor sizes included  $\leq 2$  centimeters (cm) (67%), 2–5 cm (31%),  $> 5$  cm (1.5%), and unknown (0.3%). In the NO group, 432 women received tamoxifen and 440 received anastrozole. In the N+ group, 152 women received tamoxifen and 154 received anastrozole. The median follow-up was 8.5 years. Tumor size and the Oncotype Recurrence Score (RS) were each separately statistically significant ( $p < 0.001$  each) in predicting time to distant recurrence (TTDR) in NO patients. The RS was also predictive of TTDR in N+ patients ( $p = 0.002$ ) in multivariate analyses. The number of positive nodes ( $p < 0.001$ ) and tumor size ( $p = 0.006$ ) were also statistically significant variables in multivariate analyses. The rates of distant recurrence (DR) at 9 years in the NO patients were 4% in the RS  $< 18$  group, 12% in the RS 18–30 group, and 25% in the RS  $\geq 31$  groups and in the N+ groups, 17%, 49%, and 64% respectively. The overall survival (OS) rates at 9 years in the NO patients were 88% in the RS  $< 18$  group, 84% in the RS 18–30 group, and 73% in the RS  $\geq 31$  groups and in the N+ group, 74%, 69%, and 54%, respectively. Seventy-two NO patients, 74 N+ patients and six node unknown patients experienced distant recurrence (DR). The DR rate increased linearly with an increase in RS. The risk was higher for N+ and for patients with  $\geq$  four positive nodes. There was no significant difference in the RS and risk of DR by treatment or by NO or N+. The prognostic information from the RS was

independent of the prognostic information of Adjuvant! Online, a software model that predicts the benefit of adjuvant therapy. Limitations of the study include the retrospective study design, heterogeneous patient population, and the small node-positive patient population.

In a retrospective review of a randomized controlled trial (i.e., Southwest Oncology Group (SWOG)-8814, INT-0100 study), Albain et al. (2009) investigated the ability of the Oncotype recurrence score to determine the prognosis of node-positive women (n=227) treated with tamoxifen alone and those who might not benefit from anthracycline-based chemotherapy. The study included postmenopausal women with axillary node-positive (1–3 vs.  $\geq 4$  nodes) breast cancer and either ER-positive or PR-positive tumors. Patients were randomized to treatment with tamoxifen alone for five years (n=148; 94 with 1–3 positive nodes) or to treatment with cyclophosphamide, doxorubicin, and fluorouracil followed by tamoxifen (CAF-T) (n=219; 133 with 1–3 positive nodes). Patients in this subset had a slightly lower number of positive nodes and smaller tumor size ( $< 2$  cm [n=46], 2–5 cm [n=94],  $> 5$  cm [8]) compared to the parent trial, and 11.7% were HER2 positive. The samples were analyzed using the RT-PCR Oncotype assay. The recurrence score was significantly prognostic in the tamoxifen-only group (p=0.006). No benefit was identified in CAF-T patients with a recurrence score  $< 18$  (p=0.97). There was however, an improvement in disease-free survival for those with a high recurrence score  $\geq 31$  (p=0.033). The recurrence score by treatment interaction was significant only in the first five years (p=0.029), but the cumulative benefit was present at ten years. The results of the study suggested that patients with a low recurrence score and 1–3 involved axillary lymph nodes did not benefit from anthracycline-based chemotherapy, but those with a higher recurrence score had major benefit, independent of the number of positive nodes. Although the study provided further data on the prognostic value of Oncotype for postmenopausal women with ER-positive, 1–3 node-positive breast cancer treated with adjuvant tamoxifen, the authors noted the following limitations: it is unknown if the results of the study can be applied to premenopausal women; because the study involved a subset of patients from the original trial, the benefit of CAF-T at specific recurrence score values should be interpreted with caution; “the prognostic and predictive effects of the recurrence score might differ because of the inclusion of disease-free survival events such as second primary cancers and breast recurrences”.

Using tumor samples (n=465) from a previous randomized controlled trial, Goldstein et al. (2008) conducted a clinical trial to evaluate the prognostic utility of Oncotype in either node-negative or node-positive, hormone receptor-positive breast cancer patients treated with doxorubicin-containing chemotherapy and to determine if Oncotype could more reliably predict outcomes at five years than standard clinicopathologic features. The study included pre- (41.4%) and postmenopausal (58.6%) women, HER2 positive (21.9%) and HER2 negative (44.0%) (HER2 status was unknown in 34.1% of women). Axillary node status included 56.5% negative nodes, 24.0% one positive node, 13.5% two positive nodes, and 6.1% three positive nodes. Tumor sizes included  $\leq 2.0$  cm (52.9%), 2.1–5.0 cm (42.5%), and  $> 5.0$  cm (3.6%). All patients received chemotherapy. The median follow-up was six years. The authors used an integrator that was modeled after Adjuvant! but adjusted for five-year outcomes, evaluated the concordance between RS prediction and the integrator, compared the RS predictive accuracy with the integrator, and evaluated if RS provided additional information regarding relative risk of recurrence. The results indicated that the RS was significantly predictive of recurrence in patients with and without positive nodes (p $< 0.001$ ). Approximately 3.3% of patients with a recurrence score  $< 18$  with 0–1 positive nodes experienced recurrence within five years compared to 7.9% with 2–3 positive nodes. Limitations of the study include the retrospective study design, use of an integrator tool developed by the authors, and the heterogeneous patient population.

Following a systematic review of the literature, a 2010 BlueCross BlueShield technology assessment concluded that the 21-gene OncotypeDX Breast Cancer Assay did not meet TEC criteria for gene expression profiling to aid in the selection of adjuvant chemotherapy in women with lymph-node positive breast cancer. The assessment noted that the test is not FDA approved, and the available evidence did not allow conclusions for selecting adjuvant chemotherapy in this subpopulation. There was a lack of evidence to determine if OncotypeDX improved net health outcomes and was beneficial as an established alternative. They also stated that since it has not yet been demonstrated that the 21-gene profile improves health outcomes in the investigational setting, it cannot be demonstrated whether improvement is attainable outside the investigational setting.

### **Breast Cancer Gene Expression Ratio**

The Breast Cancer Gene Expression Ratio, also known as the 2-gene ratio or HOXB13/IL17BR or H:I, is a breast cancer recurrence test proposed for use in “treatment-naïve individuals with ER-positive, lymph node

negative breast cancer". This RT-PCR assay is based on the ratio of expression of the homeobox gene-B13 (HOXB13) and the interleukin-17B receptor gene (IL17BR) (i.e., H:I expression ratio), and performed in formalin-fixed, paraffin-embedded tumor tissue. HOXB13 is rarely expressed in normal breast tissue, is expressed in cancerous breast cells, and is negatively regulated by estrogen. IL17BR is often lost in the presence of cancer cells and is positively regulated by estrogen. The results are reported as a normalized H:I expression ratio along with a categorization of low or high risk for breast cancer recurrence at 5 years. According to Quest Diagnostics, the H:I ratio serves as a continuous marker of recurrence risk in untreated patients and "should not be used to predict response to therapy. The results should be used in light of other relevant clinical and laboratory findings". The test is licensed by Quest Diagnostics (Quest Diagnostics, 2009; Marchionni, et al., 2008; Harris, et al., 2007).

The results of H:I clinical trials have indicated that "higher levels of HOXB13 and lower levels of IL17BR expression predict distant tumor recurrence in tamoxifen-treated patients with ER-positive breast cancer" and that the "H:I expression is predictive of response to first-line tamoxifen monotherapy in ER-positive breast cancer patients with metastatic disease" (Wang, et al., 2007).

**Literature Review:** The evidence in the peer-reviewed literature does not support the accuracy and clinical utility of Breast Cancer Gene Expression Ratio as a predictor of tumor recurrence. The impact of this test on meaningful health outcomes has not been established. Studies are retrospective in design and included heterogeneous patient populations. The outcomes varied based on whether or not the patient was ER-positive, ER-negative, lymph-node positive, or lymph-node negative, and the HER2 status. Results of clinical trials included an overall accuracy of 81%, positive predictive value of 82-87%, negative predictive values of 75-82%, and recurrence rates of low risk patients at 17-25%. Studies comparing the 2:1 Ratio to conventional risk classifiers are lacking.

Jerevall et al. (2008) conducted a study to determine if the 2-gene ratio could predict the benefit of five years vs. two years of tamoxifen treatment of 264 postmenopausal patients and investigate prognostic effects of the ratio in 93 systematically untreated premenopausal patients. Tumor samples from two different independent studies were used. The patients underwent surgery and radiotherapy if lymph node positive (LNP). A correlation was found between a high H:I ratio and larger tumors, high histological grade, and the lack of ER and progesterone receptors, and a positive HER2. IL17BR alone was correlated with factors related to poor prognosis. The lower IL17BR was associated with markers of worse outcomes. The survival curves for ER-negative postmenopausal women did not reveal any significant differences ( $p=0.21$ ). A benefit from prolonged duration of tamoxifen was seen in postmenopausal ER-positive women with a lower H:I ratio ( $p=0.021$ ). Likewise, a low HOXB13 with five years of tamoxifen was proven beneficial ( $p=0.010$ ), and the benefits of longer endocrine treatment reached borderline significance ( $p=0.061$ ). For untreated premenopausal women, a high IL17BR had better recurrence-free survival compared to a low expression ( $p=0.12$ ), which was similar for the H:I ratio ( $p=0.12$ ). Outcomes of the study indicated that a high H:I ratio or high HOXB13 are indicative that a patient will less likely respond to endocrine therapy and that IL17BR may be an independent prognostic factor.

Jansen et al. (2007) retrospectively measured the H:I expression levels in primary, operable tumor specimens to determine the relationship of the H:I ratio to tumor aggressiveness and response to tamoxifen. The subjects included women ( $n=1252$ ), less than age 40 to over 79 years, premenopausal ( $n=537$ ), postmenopausal ( $n=715$ ), tumor sizes T1-T3, lymph node negative (LNN) and LNP, with low and high estrogen receptor (ER) and progesterone receptor (PR) status. The mRNA expression levels were measured in all 1252 specimen. The HOXB13 level showed an inverse association to IL17BR ( $p<0.001$ ). In 448 tumors, the HOXB13 levels were significantly below detection in ER-positive tumors compared to ER-negative tumors ( $p<0.001$ ). With the exception of tumor size, IL17BR was significantly, positively associated with age and menopausal status and negatively associated with grade and nodal status. The median expression level of HOXB13 was higher in poorly differentiated tumors, and lower in ER-positive tumors compared to ER-negative tumors. In all tumors, the H:I ratio measured as a univariate log-transformed continuous variable was associated with a poor DFS ( $p<0.001$ ) and poor overall survival (OS) ( $p<0.001$ ). To test for relation between expression ratio and LNN, 468 ER-positive tumors were analyzed, of whom 217 patients had a relapse during follow-up. In univariate analysis, the H:I ratio was significantly associated with a poor DFS ( $p=0.001$ ) and a poor OS ( $p<0.001$ ). The H:I prognostic value was assessed in 151 ER-positive lymph node positive patients and was associated with a poor DFS ( $p=0.023$ ) and poor OS ( $p<0.001$ ). In 193 ER-positive tumor patients treated with tamoxifen, the H:I ratio was related to a poor response ( $p=0.027$ ), a short progression-free survival (PFS) ( $p<0.001$ ), and poor postrelapse

survival (PRS) (<0.001). The study indicated that high H:I levels are associated with tumor aggressiveness and tamoxifen monotherapy failure.

Using RT-PCR, Wang et al. (2007), measured HOXB13, IL17BR and CHDH gene expression and correlated it with ER and PR, known biomarkers of tamoxifen response, and HER2 expression. Formalin-fixed, paraffin-embedded tumor samples were prospectively collected from 75 consecutive ER-positive and 73-consecutive ER-negative breast cancer patients. A high HOXB13 was observed in 50% of ER-positive and 67% of ER-negative tumors ( $p=0.047$ ). IL17BR and CHDH expressions were higher in ER-positive tumors ( $p=1.8e-07$ ). HOXB13 correlated positively with HER2 status in ER-positive tumors ( $p=0.021$ ) and IL17BR and CHDH negatively correlated with HER2 status, more so in ER-positive tumors ( $p=0.0020$ ;  $p=0.026$ , respectively). The study indicated that HOXB13 and IL17BR are regulated by estrogen, but does not formally establish that they are direct targets of estrogen.

Goetz et al. (2006) studied the association of the H:I ratio to clinical outcomes of relapse and survival in ER-positive breast cancer patients enrolled in the North Central Cancer Treatment Group adjuvant tamoxifen trial (NCCTG-89-30-52), a randomized phase III trial involving women with resected ER-positive breast cancer. Postmenopausal women with node-negative disease were T1C or T2N0M0 and any age. Women who were node-positive were at least age 65 years, tumor stage T1-T2N1M0. Follow-up ranged from 5.7–13.6 years (median, 11 years). Tumor blocks were obtained from 211 patients from the tamoxifen only arm and H:I profiles were obtained from 106 patients. In LNP patients ( $n=86$ ), the H:I ratio was not associated with relapse or survival, but in the LNN patients ( $n=130$ ), a high ratio was associated with a worse relapse-free survival (RFS) ( $p=0.031$ ), DFS ( $p=0.015$ ) and OS ( $p=0.014$ ) independent of standard prognostic markers. The study demonstrated that the H:I ratio was associated with relapse and survival in LNN breast cancer.

**HERmark<sup>®</sup> Breast Cancer Assay:** The HERmark Breast Cancer Assay (Monogram Biosciences, South San Francisco, CA) is a dimerization assay proposed to quantitatively measures HER2 total protein (H2T) and functional HER2 homodimers (H2D) to aid in stratifying patients with breast cancer who are likely to respond to trastuzumab (Herceptin<sup>®</sup>)-containing therapy. The test uses two monoclonal antibodies specific for epitopes on the HER2 receptor which results in both antibodies binding to the same HER2 receptor. Using VeraTag<sup>™</sup> (Monogram Biosciences), a proximity-based method, the concentration of HER2 in the sample is quantified using a fluorescent tag. HERmark measures a distribution of HER2 expression over a large range of receptors/cells. Immunohistochemistry (IHC) (scored as 0, 1+, 2+, and 3+), and fluorescence in situ hybridization (FISH) are the two standard testing methods for assessing HER2 expression. According to Huang et al. (2010), neither IHC nor FISH “is a perfect predictor of response to trastuzumab, and both tests are affected by interlaboratory variability”. HERmark is performed using formalin-fixed, paraffin-embedded (FFPE) tissue samples. Results are reported as HER2 negative (i.e., < 5th percentile of samples classified as HER2 positive by reference methods), positive (i.e., > 95% of samples classified as HER2 negative by reference methods) or equivocal (i.e., overlap of HER2-positive and negative distributions, 95th percentile). The test is Clinical Laboratory Improvement Amendments (CLIA) validated and performed in a College of American Pathologists (CAP)-certified clinical reference laboratory (Huang, et al., 2010; Monogram Biosciences, Inc., 2008). Evidence in the published peer-reviewed scientific literature has not established the accuracy, clinical utility, and beneficial impact on health outcomes of this evolving technology.

In a study comparing HERmark to IHC and FISH in patients with invasive breast cancer ( $n=237$ ), Huang et al. (2010) reported that the overall concordance between H2T and IHC was 67%. The positive and negative concordance between HERmark and IHC were 95% and 92%, respectively. When the equivocal cases were excluded, overall concordance was 98%. The concordance values between the negative, equivocal, and positive results from FISH compared to HERmark ranged from 39%–67%. The authors noted that “clinical studies are clearly needed to understand the relationship between quantitative HER2 expression and homodimer measurements with clinical outcomes in patients with breast cancer treated with anti-HER2 therapy”. It was also stated that “the limited number of trastuzumab-treated cases in this study does not provide adequate statistical power for sufficient analysis of correlating the HERmark status and patient response to trastuzumab”.

Lipton et al. (2010) conducted a study to quantitatively measure HER2 expression in 102 formalin-fixed paraffin-embedded (FFPE) breast tumor specimens using HERmark and compared the results to local IHC and central FISH results, along with clinical outcomes. The specimens were from a study population of women diagnosed with metastatic breast cancer as IHC 3+ ( $n=95$ ) or IHC 2+/FISH positive ( $n=5$ ) or IHC unknown/FISH positive ( $n=2$ ) who were prospectively observed during trastuzumab-based therapy. Follow-up ranged from 11.8–77.9

months (mean 34 months). Discordance was reported in three of 22 FISH-negative patients who were H2T expression high and 10 of 76 FISH-positive patients who were H2T expression low. The patients with H2T expression low experienced a significantly shorter time to progression on trastuzumab compared to FISH-positive patients with high total HER2 protein expression. The authors noted that “an important limitation” of this analysis was that they did not have enough material to gather central IHC data for the discordant subgroup of patients. Other author-noted limitations included the small sample size, retrospective study design, “the lack of a trastuzumab-untreated control arm, the lack of central IHC measurements for all patients to confirm that some of the cases included were not HER2 IHC false positives, and the heterogeneous chemotherapy to which patients were exposed”.

### **MammaPrint**

MammaPrint is a deoxyribonucleic acid (DNA) microarray assay used to assess breast tumors  $\leq 5$  cm in women less than age 61 years who have stage I or stage II, invasive (infiltrating) breast cancer with ER-positive or ER-negative receptors, and are lymph node negative. From a fresh-frozen sample, the test extracts mRNA and hybridizes it to a DNA microarray. The specific genes expressed in the tumor tissue and the resulting gene expression profiles are proposed to be predictive of the risk of metastasis. MammaPrint was validated in the TRANSBIG collaborative study (n=302) (Agendia, 2008; Buyse, et al., 2006).

**U.S. Food and Drug Administration (FDA):** In February 2007, the FDA approved the first molecular prognostic test, MammaPrint (Agendia BF, Amsterdam, The Netherlands), “a qualitative in vitro diagnostic test, performed in a single laboratory, using the gene expression profile of fresh breast cancer tissue samples to assess a patient’s risk for distant metastasis (up to 10 years for patients less than 61 years old, up to 5 years for patients  $\geq 61$  years)”. Per the FDA approval, “the test is performed for breast cancer patients, with Stage I or Stage II disease, with tumor size  $\leq 5.0$  centimeters (cm) and who are lymph-node negative. The MammaPrint result is indicated for use by physicians as a prognostic marker only, along with other clinicopathological factors” (FDA, 2009; FDA, Feb 2007). The FDA did not require prospective clinical trials for the approval.

**Literature Review:** The evidence in the published peer-reviewed scientific literature does not support the accuracy and clinical utility of MammaPrint for the prognosis of breast cancer. Studies have included retrospective analysis of tissue samples from case series with heterogeneous patient populations and variable follow-up lengths. It is yet to be proven in prospective, clinical trials that MammaPrint improves stratification beyond what is currently available through clinical and histopathological assessment or that it provides meaningful improvements in health outcomes.

Five-year from surgery to distant metastasis (DMFS) rates have been reported at 93%-100% in low-risk groups and 80% in high-risk groups. The ten-year DMFS ranged from 87–88% in low-risk groups and 69–72% in high risk groups. The five-year and ten-year breast cancer specific survival (BCSS) in low-risk groups were 99% and 87%, respectively and 88% and 72%, respectively in high-risk groups. The negative predictive value for distant metastasis-free survival at five years in low risk groups was 100% and the negative predictive value for distant metastasis-free survival at five years in high risk groups was 94%. Reported positive predictive values have ranged from 9.8%–12% for low risk. Discordance in up to approximately one-third of the patients between the Signature and the clinical risk index used (e.g., Adjuvant!) has been recorded (Mook, et al., Apr 2010; Ishitobi, et al., 2010; Wittner, et al., 2008; Van De Vijver, et al., 2002). The sensitivity of the MammaPrint has been reported at 85–92% with a specificity of 42–86% (California Technology Assessment Forum, 2010).

Mook et al. (May 2010) evaluated the accuracy of the 70-gene MammaPrint signature on 964 frozen samples from seven previously reported studies on women with pT1 tumors ( $\leq 2$  cm). A total of 139 patients had a pT1a tumor ( $\leq 10$ mm), 825 had a pT1c (11–20 mm) tumor, 693 patients had node-negative cancer, and 263 patients had node-positive cancer. Of the 964 patients, 552 received no adjuvant systemic therapy, 408 patients received endocrine- and/or chemotherapy, and adjuvant systemic therapy was unknown for four patients. Follow-up ranged from 0.2–25.2 years (median 7.2 years) and during this period 154 patients developed distant metastases and 130 patients died of breast cancer. Twenty-five patients died of other causes. Outcomes included time from surgery to distant metastasis (DMFS), and time from surgery to breast cancer related death (i.e., breast cancer specific survival [BCSS]). MammaPrint classified 525 tumors as good prognosis and 439 as poor prognosis. For the good prognosis group, the 10-year DMFS rate was 87% and the BCSS was 87%. The probability of remaining free of distant metastases at 5 years was 95% and at 10 years was 87%. The five- and ten-year BCSS was 99% and 91%, respectively (p<0.001). The DMFS and BCSS for the poor prognosis group was 72% each at ten years. MammaPrint was an independent prognostic factor for BCSS at 10 years (p<0.001)

and additionally, predicted DMFS at 10 years ( $p=0.04$ ) for 139 patients with pT1ab cancers. The probability of remaining free of distant metastases at 5 years was 80% and at 10 years was 72%. The five- and ten-year BCSS was 88% and 72%, respectively ( $p<0.001$ ). Of the patients with pT1ab tumors, 40% were classified as poor prognosis. The signature retained its prognostic value in untreated patients and was an independent prognostic factor in 788 ER-positive patients for DMFS and BCSS ( $p<0.001$ , each). It was noted that a potential limitation of the study was the heterogeneous patient population, especially related to years of diagnosis and adjuvant therapy and some patients had been previously treated based on the outcome of MammaPrint. Another limitation of the study is the small patient populations in the T1ab subgroups.

In the first study to assess the prediction of adjuvant chemotherapy using MammaPrint, Knauer et al. (2010) evaluated the predictive value of this test for 315 patients treated with endocrine therapy (ET) compared to 226 patients treated with endocrine plus chemotherapy (CT). Specimens were selected from a database from seven previously reported studies and included patients with unilateral stage pT1-3, node 0–1 breast cancer with no distant metastasis. Patients were ER-positive (90%) and PR-positive (69%). Follow-up ranged from 0.2–25.2 years (median 7.2 years). At five years, 52 patients had distant metastases and 33 had died of the disease. MammaPrint classified 252 patients as low risk and 289 patients as high risk. At five years, the BCSS for the low-risk group was 97% for the ET group and 99% for the ET/CT group ( $p=0.62$ ) and the DDFS was 93% and 99%, respectively. The BCSS for the high-risk group was 81% for the ET group and 94% for the ET/CT group ( $p<0.01$ ). The DDFS was 76% and 88%, respectively. Statistically comparing relative and absolute differences in survival revealed that adding CT to patients in the high-risk group could prevent 33 events per 1000 patient years, resulting in a number needed to treat of 30. Significant survival benefit was shown with the addition of CT in the high-risk group. Patients in the low-risk group gained no significant benefit from the addition of chemotherapy. Limitations of the study include the retrospective design, small patient populations, and difference in CT regimens.

Bueno-de-Mesquita et al. (2007) conducted a prospective study to assess the feasibility of implementation of the MammaPrint assay in a community-based setting and to determine its effect on adjuvant systemic treatment decisions compared to treatment advice provided by the Dutch Institute for Healthcare Improvement (CBO) and other guidelines. The Microarray Prognostics in Breast Cancer (RASTER) study included 427 viable samples that met inclusion criteria from women, under age 61 years, with primary, unilateral, operable, invasive adenocarcinoma of the breast. Follow-up ranged from 0.3–36.4 months (median 14 months). The study protocol was amended at the end of 2004 to include women less than age 55 years. MammaPrint (i.e., signature) identified 219 patients with good prognosis and 208 patients with poor prognosis compared to 184 poor prognosis identified by the CBO guidelines which was discordant with 128 signature results. Adjuvant therapy would be initiated in 203 patients based on CBO guidelines; 265 patients based on MammaPrint results; and 259 patients based upon CBO, MammaPrint and patient preferences. Adjuvant! Online identified 294 patients with poor prognosis (discordant with 160 signature patients) and St. Gallen guidelines with the signature identified 353 patients with poor prognosis. The Nottingham Prognostic Index with the signature identified 179 poor-prognosis patients, discordant with 117 patients. Discordance was noted in approximately one-third of the patients between the signature and the clinical risk index regardless of the index used.

The California Technology Assessment Forum (CATF) (2010) conducted a systematic review of the literature to evaluate the evidence of MammaPrint. Earlier studies reported a sensitivity of 85%–92% and a specificity of 73%–86%. The Forum noted that the strength of the association for DMFS was strongest in studies with short-term follow-up and weakest in studies with long-term follow-up, suggesting that MammaPrint is primarily a risk factor for metastasis during the first-five years of follow-up. The authors concluded that there was insufficient evidence to demonstrate that MammaPrint improves net health outcomes and is as beneficial as established alternatives. Improvement outside of the investigational setting has not been reported. Therefore the CATF does not recommend MammaPrint.

### **Rotterdam Signature 76-Gene Panel**

The Rotterdam Signature 76-gene panel was developed to assist physicians to predict the likelihood that a patient with early-stage breast cancer will develop a metastasis. The microarray assay represents a prognostic molecular marker that is proposed to be used with all lymph node negative (LNN) breast cancer patients, regardless of age, tumor size and grade, or ER status. Sixty genes evaluate ER-positive samples and 16 genes evaluate ER negative samples. The 76-gene signature analyzes fresh frozen tumor samples and classifies patients as having a gene expression signature associated with either a low or high risk of developing metastatic disease. The test is not yet commercially available.

**Literature Review:** The evidence in the published peer-reviewed scientific literature does not support the accuracy and clinical utility of the Rotterdam Signature test, nor have the data shown an impact on meaningful health outcomes in predicting the risk of breast cancer recurrence. The reported sensitivity of the test ranged from 80%–93% and the specificity ranged from 40–48%. Reported five-year distant metastasis-free survival rates included 90%–98% for low-risk patients and 74%–76% for high-risk patients. The 10-year rates were 94% for low-risk patients and 65%–72% for high-risk patients. The positive predictive value was 38%, and the negative predictive value was 94% (Desmedt, et al., 2007; Foekens, et al., 2006; Wang, et al., 2005).

Using the 76-gene signature, Zhang et al. (2009) assessed the benefit of adjuvant systemic tamoxifen therapy (n=136) vs. no therapy (n=164). Frozen tumor specimens from women with lymph node negative, estrogen positive breast cancer from two matched cohorts were analyzed. Follow-up time of surviving patients ranged from 29–193 months (median 90 months). When applied to the 136 tamoxifen-treated patients, the gene signature stratified the patients into high-risk and low-risk groups. The 10-year distant metastasis-free survival (DMFS) rate of the low-risk group was 96% compared to 77% for the high-risk group. The low-risk tamoxifen-treated patients had a non-significant (7.2%) better 10-year DMFS than the untreated patients. When the gene signature was applied to all patients, the low-risk group (n=116) showed a 2.7% non-significant 10-year DMFS benefit from tamoxifen therapy. The high-risk group (n=184) showed a significant (p=0.0318) 10-year DMFS absolute benefit of 12.3% with tamoxifen. Also, in the high-risk group, the 10-year DMFS for untreated patients was 64.7% compared to 77.0% for tamoxifen-treated patients. The authors noted that “caution should be taken to decisively interpret these results as an effect of tamoxifen therapy because the included patients did not participate in a randomized trial, but received local treatment according to institutional guidelines effective at the time of surgery”.

Desmedt et al. (2007) reported the results of a study conducted by TRANSBIG (i.e., network for improved treatment tailoring established by the Breast International Group [BIG] [TRANSBIG]), a transnational research network involving 40 partners in 21 European countries (TRANSBIG, 2006) to validate the 76-gene prognosis signature and to compare the signature outcome with clinical risk assessment. Frozen tissue samples (n=198) from a previous study (Buyse, et al., 2006) were obtained from women, age less than 61 years, with node negative, T1-T2 ( $\leq 5$  cm) tumors. Median follow-up was 14 years, distant metastases occurred in 51 patients, and 35 patients demonstrated progression within five years. Based on the signature, patients were identified as high (n=143) or low (n=55) genomic risks and as high (n=152) and low (46) clinical risks based upon Adjuvant! Online. The low genomic risk included 14 ER-negative patients, whereas there were none in the low-risk clinical group. Fourteen low-risk genetic patients were ER-negative compared to 50 high-risk genetic patients. The gene signature actual five- and ten-year time to distant metastases (TDM) was 98% and 94%, respectively, for the good profile group and 76% and 73%, respectively for the poor profile group. The overall survival for the good profile group was 98% and 87% at five and ten years, respectively and 84% and 72%, respectively for the poor profile group. The five- and ten-year sensitivity for TDM was 97% and 93%, respectively, with a 34% and 31%, respectively for specificity. The HR was 5.78 (95% confidence interval [CI], 1.78–18.80) for TDM and 2.87 (95% confidence interval [CI], 1.21–6.82) for OS. Adjusted for clinical risk, the global HR was 5.11 (1.57–16.67) for TDM and 2.55 (1.07–6.10) of OS). In the low genomic and low clinical risk groups, no patient developed distant metastasis.

### **Other Gene Assays**

Additional gene assays have been proposed to aid in treatment planning and predicting prognosis of women with various types of breast cancer. The evidence in the published peer-reviewed literature does not support the accuracy or the clinical utility of these assays. The role of these assays in the management of individuals with breast cancer and their impact on health outcomes has not been established. Some assays are awaiting FDA approval, while others are still in the developmental stages and are not commercially available.

**Breast Bioclassifier™:** Breast Bioclassifier (AURA, Salt Lake City, UT) is a 55-gene (i.e., 50 classifier genes and five control genes) RT-PCR assay that classifies ER-positive and ER-negative breast cancers to help predict outcomes. The test provides biologic subtypes of breast cancer (i.e., luminal-A, luminal-B, HER2, and basal-like) and reports outcomes on as a continuous risk score (ARUP, 2010; Nasser, 2009; Ross, et al., 2008).

**Breast Cancer Gene Expression Prognosis Profile (BreastOncPx™):** BreastOnc is a 14-gene signature proposed for use in lymph node negative, ER-positive patients to estimate the likelihood of recurrence including distant metastasis (Laboratory Corporation of America, 2010). Tutt et al. (2008) reported that the sensitivity and

specificity of the metastasis score (MS) high and low risk groups to predict distant metastases were 96% and 43% at five years, respectively, and 93% and 46% at ten years, respectively. Sensitivity and specificity of the MS risk groups to predict death from any cause at 10 years were 84% and 45%, respectively.

**eXagen™:** eXagenBC (eXagen Diagnostics, Inc., Albuquerque, NM) is a fluorescence in situ hybridization (FISH) assay proposed for assessing breast cancer metastases in women with newly diagnosed, early stage invasive ductal breast cancer. The test has been submitted for FDA approval and is currently only available in investigational use (eXagen, 2008; Ross, et al., 2008).

**Mammostrat®:** Mammostrat (Applied Genomics, Inc. [AGI], Huntsville, AL) is a prognostic test that uses immunohistochemistry stains to stratify estrogen receptors using five antibodies. According to AGI, the test “measures the presence of five proteins that are thought to be associated with cell cycle regulation (p53 and HTF9C), differentiation (CEACAM5), hypoxia (NDRG1), and nutrient supply (SLC7A5)”. The test is proposed for postmenopausal, node negative, ER-positive women who will receive hormonal therapy and may be candidates for adjuvant chemotherapy. The test identifies low-, moderate- and high-risk groups. Mammostrat is currently available from a centralized CLIA laboratory. AGI is pursuing FDA approval (AGI; Ross, et al., 2008; Ring, et al., 2006).

Bartlett et al. (2010) conducted a validation study to evaluate the efficacy of the Mammostrat assay using a cohort of patients (n=1540) with breast cancer and reported that increased Mammostrat scores were associated with reduced distant recurrence-free survival (DRFS); relapse-free survival (RFS), and overall breast cancer specific survival (OS). Increased Mammostrat scores were found to be significantly ( $p < 0.00001$ ) associated with reduced DRFS, RFS, and OS in ER-positive breast cancer patients. The risk score was independent of conventional risk factors for DRFS, RFS and OS. The 10-year recurrence rates in tamoxifen-treated, node-negative patients were  $7.6 \pm 1.5\%$  in the low-risk group and  $20.0 \pm 4.4\%$  in the high-risk group.

**Breast Cancer Index<sup>SM</sup>:** Breast Cancer Index (bioTheranostics, San Diego, CA) is a combination of the Theros H/I<sup>SM</sup> and the bioTheros MGI<sup>SM</sup>. The Theros H/I is a two-gene index that stratifies ER-positive cancer for endocrine therapy benefit. The Theros MGI is a five-gene index that provides quantitative and objective molecular assessment of tumor grade and proliferative rate. MGI discriminates between tumor grades 1 and 3 and reclassifies grade 2 tumors into low- or high-risk. It is also a prognostic indicator for ER-positive patients regardless of nodal status and indicative of response to chemotherapy. Each test stratifies breast cancers as low or high for recurrence. It is proposed that by combining these two individual test results, one would obtain independent and complementary prognostic information. Results using the combined testing are reported as low-, intermediate- or high-risk for recurrence. The H/I and the MGI tests can be used independently. bioTheranostics is a CLIA-certified laboratory (bioTheranostics, 2010).

Additional gene-profiling assays under investigation include the Invasiveness Signature™ (Oncomed Pharmaceuticals, Redwood City, CA). This test consists of 186 genes and is designed for node negative, node positive, ER-negative and ER-positive breast cancers. Nuvera Bioscience, Inc., (Woburn, MA) is developing the NuvoSelect™ eRx 200-gene assay to predict response to endocrine therapy and the NuvoSelect cRx, a 207-gene predictor of taxane-based chemotherapy response (Nuvera Biosciences, 2010; Ross, 2008; Liu, et al., 2007).

### **Systematic Reviews/Technology Assessments**

ECRI Institute (2008) conducted a systematic review of the literature and concluded “existing studies provide clinical validation for the ability of the Oncotype DX assay and the MammaPrint assay to predict tumor recurrence and response to chemotherapy. However, the studies are insufficient to allow one to draw strong conclusions regarding the clinical utility of these assays for guiding treatment decisions for patients with early-stage invasive breast cancer”.

Marchionni et al. (2008) conducted a systematic review to summarize studies on Oncotype DX (n=10), MammaPrint (n=4) and H:I expression ratio (n=6). Information was reviewed regarding clinical characteristics of the patients, tumor characteristics, and whether the marketed test or underlying signature was evaluated. The authors concluded that these technologies “show great promise”, but more information is needed regarding “the extent of improvement in prediction, in whom the tests should be used and how test results are best incorporated into decision making about breast cancer treatment”. They also noted that the “relationship of

predicted-observed risk in different populations”, “incremental contribution over conventional predictors, optimal implementation and relevance to patients receiving current therapies” need further study.

The BlueCross BlueShield Association Technology Evaluation Center (TEC) published an assessment (2008) on the role of gene expression profiling in the treatment of breast cancer. Included in the report was a review of studies published on Oncotype DX, MammaPrint and Breast Cancer Gene Expression Ratio assays. Regarding Oncotype DX, the report stated that the evidence is sufficient to permit conclusions regarding improved net health outcomes in lymph-node-negative, ER-positive breast cancer patients who met the specific trial enrollment criteria and “provides information about the risk of recurrence that is incremental to conventional classifiers used to predict risk. They also stated that additional studies are needed due to several limitations to the evidence. In relationship to MammaPrint and Breast Cancer Gene Expression Ratio, the report stated that the evidence is insufficient to determine if these assays improve net health outcomes in women with early stage breast cancer.

### **Professional Societies/Organizations**

**American Society of Clinical Oncology (ASCO):** In a 2007 update of the recommendations for the use of tumor markers in breast cancer, ASCO stated 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. Oncotype DX may be used to identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy”. In addition, patients with high recurrence scores appeared to achieve relatively more benefit from adjuvant chemotherapy than from tamoxifen. They also notes that there was insufficient data to comment on whether these conclusions generalize to hormonal therapies other than tamoxifen, or whether this assay applies to other chemotherapy regimens. The precise clinical utility and appropriate application for other multiparameter assays, such as the MammaPrint assay, the Rotterdam Signature, and the Breast Cancer Gene Expression Ratio are under investigation.

**Evaluation of Genomic Applications in Practice and Prevention (EGAPP):** The EGAPP Working Group (2009) published recommendations on the use of gene expression profiling for the treatment of women with breast cancer. The review included Oncotype, MammaPrint, and the Breast Cancer Gene Expression Ratio assay. EGAPP concluded that they “found no direct evidence linking tumor gene expression profiling of women with breast cancer to improved outcomes”. Regarding clinical validity, they did state that they “found adequate evidence regarding the association of the Oncotype DX Recurrence Score with disease recurrence and adequate evidence for response to chemotherapy”. Regarding MammaPrint, The EGAPP stated that they found “adequate evidence to characterize the association of MammaPrint with future metastases, but inadequate evidence to assess the added value to standard risk stratification, and could not determine the population to which the test would best apply”. The recommendations stated that these tests have potential for benefit and for harm.

**National Comprehensive Cancer Network (NCCN):** NCCN (2010) discusses the use of gene expression profiling in the management of breast cancer patients and proposes that this technology will play an important role as a prognostic tool in the future. NCCN states “While many of the DNA microarray technologies are able to stratify patients into prognostic and/or predictive subsets on retrospective analysis, the gene subsets appear to differ from study to study, and prospective clinical trials testing the utility of these techniques have yet to be reported.” Pending the results of the TAILORx and MINDACT clinical trials, the NCCN Panel considers Oncotype DX as an option for evaluating primary tumors 0.6–1.0 cm with unfavorable features or > 1 cm and node-negative, hormone-receptor positive, HER2-negative, and axillary node negative which includes micrometastasis  $\leq$  2.0 millimeters. In this subpopulation, the recurrence score may assist in estimating the likelihood of recurrence and benefit from chemotherapy. They stress that the recurrence score should be used “for decision making only in the context of other elements of risk stratification”. These recommendations are based upon nonuniform NCCN consensus based on lower-level evidence, including clinical experience.

### **Summary**

When used as a complementary decision-making tool, in combination with other clinical indicators (e.g., tumor size and grade, hormone receptor status, HER2 status), Oncotype DX may provide clinical utility to determine whether or not a specific subset of woman with low-risk indicators might benefit from adjuvant chemotherapy. Oncotype DX is not indicated as a stand-alone test to be solely relied upon for withholding chemotherapy, nor is it indicated for use in high-risk or intermediate-risk patients (e.g., human epidermal growth factor receptor 2 [HER2]-positive or ER-negative).

The clinical utility of other genetic expression assays (e.g., Breast Cancer Gene Expression Ratio, HERmark<sup>®</sup> Breast Cancer Assay MammaPrint, Rotterdam Signature 76-Panel) in the treatment of breast cancer has not yet been established through well-designed clinical trials. Supporting data on the use of gene expression assays in men and repeat assays after the initial assessment are lacking.

## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

**Covered when medically necessary:**

CPT <sup>®*</sup> Codes	Description
84999 <sup>†</sup>	Unlisted chemistry procedure

HCPCS Codes	Description
S3854 <sup>†</sup>	Gene expression profiling panel for use in the management of breast cancer treatment

**†Note:** Covered as medically necessary when used to report the Oncotype DX<sup>™</sup> Breast Cancer Assay for the specific medical necessity criteria noted above. All other indications and other assays of genetic expression in breast tumor tissue are considered experimental/investigational/unproven and not covered.

ICD-9-CM Diagnosis Codes	Description
174.0-174.9	Malignant neoplasm of female breast
233.0	Carcinoma in situ of breast
V10.3	Personal history of malignant neoplasm, breast
V86.0	Estrogen receptor positive status (ER+)

\*Current Procedural Terminology (CPT<sup>®</sup>) © 2010 American Medical Association: Chicago, IL.

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## Policy History

<b>Pre-Merger Organizations</b>	<b>Last Review Date</b>	<b>Policy Number</b>	<b>Title</b>
CIGNA HealthCare	3/15/2008	0298	Assays of Genetic Expression in Tumor Tissue as a Prognosis in Patients with Breast Cancer
Great-West Healthcare	11/30/07	05.303.02	Genetic Testing, Breast Cancer Assay of Genetic Expression

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.