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# Genetic Testing: Gene Expression Profile Testing for Breast Cancer

MEDICAL POLICY NUMBER: 47

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**INSTRUCTIONS FOR USE:** Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

**SCOPE:** Providence Health Plan, Providence Health Assurance, and Providence Plan Partners as applicable (referred to individually as “Company” and collectively as “Companies”).

## PLAN PRODUCT AND BENEFIT APPLICATION

Commercial

Medicaid/OHP\*

Medicare\*\*

### \*Medicaid/OHP Members

Notice to Medicaid Policy Readers: For comprehensive rules and guidelines pertaining to this policy, readers are advised to consult the Oregon Health Authority. It is essential to ensure full understanding and compliance with the state's regulations and directives. Please refer to OHA's prioritized list for the following coverage guidelines:

Oncotype, EndoPredict, MammaPrint: Guideline Note 148 - Lines 157,184,191,229,262,271,329

*Oregon:* Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

### \*\*Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered “**not medically necessary**” for Medicare members.

## COVERAGE CRITERIA

- I. The use of Oncotype DX® Breast (RS), MammaPrint®, Prosigna™ (PAM50), or EndoPredict® gene expression profiling tests to guide adjuvant chemotherapy treatment decisions in patients with primary breast cancer may be considered **medically necessary** when **all** of the following criteria (A.-F.) are met:
  - A. No repeat testing is performed on the same sample when a result was successfully obtained; **and**
  - B. No previous gene expression assay is performed on the same sample when a result was successfully obtained; **and**
  - C. Patient has a diagnosis of invasive breast cancer (Stage I, II, or IIIa); **and**
  - D. Estrogen receptor (ER) and/or progesterone (PR) receptor positive; **and**
  - E. HER2-negative (please see [Policy Guidelines](#) below regarding interpretation of HER2 status); **and**
  - F. Node negative (pN0), pN1mi (micrometastasis  $\leq 2$  mm of an axillary node), or N1 (less than 4 nodes).

- II. The use of the Breast Cancer Index<sup>SM</sup> (BCI) gene expression profiling test to guide adjuvant chemotherapy and/or extended adjuvant endocrine therapy decisions may be considered **medically necessary** when all of the following criteria are met:
- A. No repeat testing is performed on the same sample when a result was successfully obtained; **and**
  - B. No previous gene expression assay is performed on the same sample when a result was successfully obtained; **and**
  - C. Patient has a diagnosis of invasive breast cancer (Stage I, II, or IIIa); **and**
  - D. Estrogen receptor (ER) and/or progesterone (PR) receptor positive; **and**
  - E. HER2-negative (please see [Policy Guidelines](#) below regarding interpretation of HER2 status); **and**
  - F. Node negative (pN0) or pN+.
- III. The use of Oncotype DX<sup>®</sup> Breast (RS), MammaPrint<sup>®</sup>, Prosigna<sup>™</sup> (PAM50), EndoPredict<sup>®</sup> or Breast Cancer Index<sup>SM</sup> (BCI) is considered **not medically necessary** when the above criteria are not met, including, but not limited to testing in the following circumstances or for any of the following indications:
- A. Repeat testing on the same breast tumor, including the use of a different gene expression profiling test
  - B. HER2-positive
  - C. Stage 0 noninvasive cancer (ductal carcinoma in situ [DCIS])
  - D. To determine ER, PR or HER2 levels or status
- IV. All other breast cancer gene expression profiling tests are considered **not medically necessary** for any indication. Non-covered tests include, but are not limited to, the following:
- A. Blueprint<sup>™</sup>
  - B. BreastOncPx<sup>™</sup>
  - C. BreastPRS<sup>™</sup>
  - D. DCISionRT by PreludeDx
  - E. Molecular Grade Index
  - F. Oncotype DX<sup>®</sup> DCIS Score
  - G. TargetPrint<sup>®</sup>
  - H. Theralink<sup>®</sup> Reverse Phase Protein Array (RPPA) (Theralink<sup>®</sup> Technologies, Inc)

Link to [Evidence Summary](#)

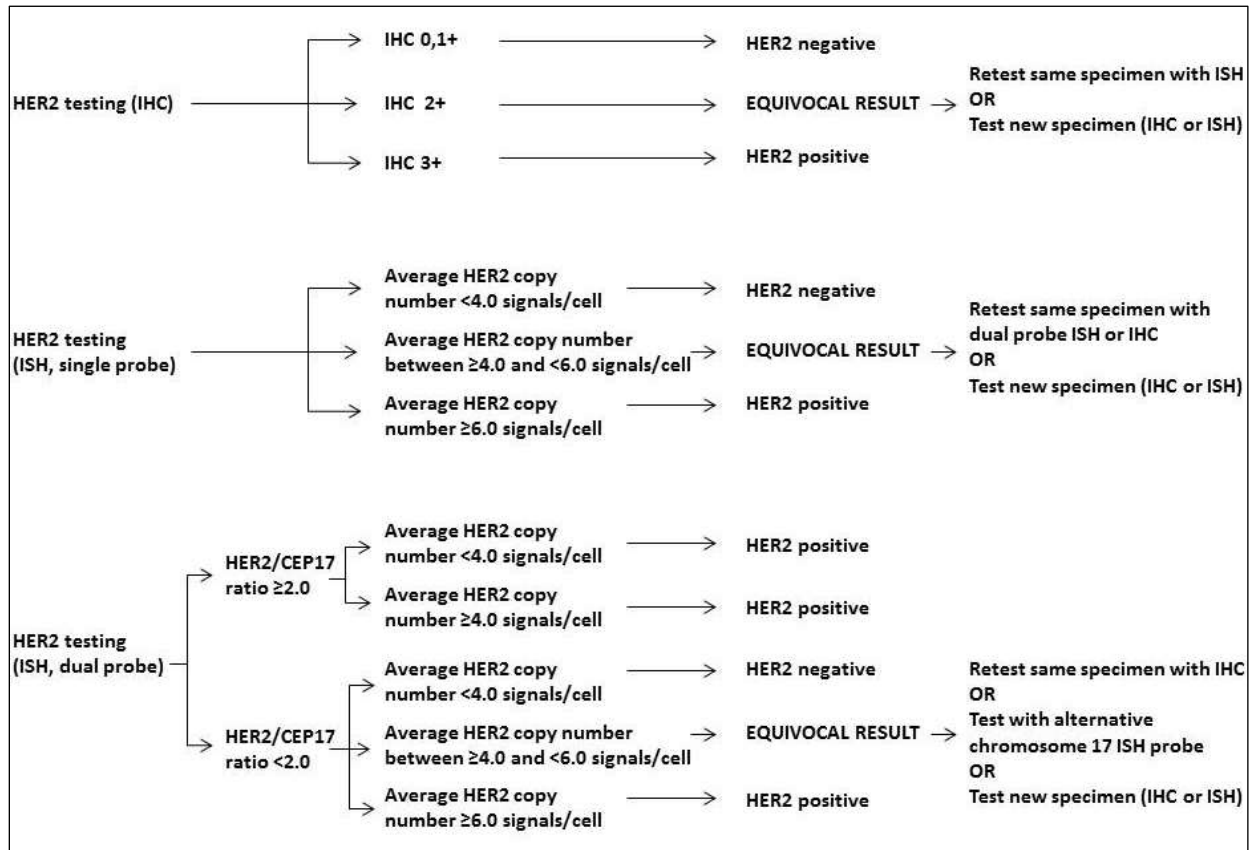
## POLICY CROSS REFERENCES

- [Genetic Counseling](#), MP316

The full Company portfolio of current Medical Policies is available online and can be [accessed here](#).

**HER2 Receptor Status**

The human epidermal growth factor receptor 2 (HER2) gene (also referred to as ERBB2) is amplified and/or overexpressed in 15% to 20% of primary breast cancers.<sup>1</sup> There are two different methods by which HER2 receptor status can be discovered; the first is immunohistochemistry (IHC) and the other is in situ hybridization (ISH). Standardized HER2 testing has been developed and updated by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP)<sup>1</sup>, and is endorsed by the current guidelines published by the National Comprehensive Cancer Network. According to these authorities, principles for HER2 testing for breast cancer and the scoring of these tests are as follows:



Adapted from the National Comprehensive Cancer Network guidelines. Breast Cancer.<sup>2</sup>

**DOCUMENTATION REQUIREMENTS**

In order to determine the clinical utility of a genetic test, the following documentation must be provided at the time of the request. Failure to submit complete documentation may affect the outcome of the review.

- Specific gene, trade or proprietary name of the test, or if a custom built test, include every gene(s) and/or component of the test
- Name of laboratory where the testing is being conducted or was conducted

- Clinical notes to include the following:
  - Documentation of [genetic counseling](#) as required in the policy criteria below which includes how test results will impact clinical decision making
  - Reason (indication) for performing test, including the suspected condition
  - Existing signs and/or symptoms related to reason for current test request
  - Prior test/laboratory results related to reason for current test request
  - Family history, if applicable
  - How results from current test request will impact clinical decision making
- All relevant CPT/HCPCS codes billed

## BACKGROUND

### Early-Stage Breast Cancer and Treatment

Breast cancer is one of the most common malignancies of women and the second leading cause of cancer-related deaths in women. The treatment of localized early-stage invasive breast cancer usually includes surgery and subsequent radiation therapy, often done in conjunction with chemotherapy or other drug therapies either before or after surgery. Treatment of ductal carcinoma in situ (DCIS) is usually breast-conserving surgery (BCS) or mastectomy. If the DCIS is hormone receptor-positive (ER-positive or PR-positive), adjuvant treatment with tamoxifen (for any woman) or an aromatase inhibitor (for women past menopause) may be considered.

After primary surgical treatment, patients may be treated systemically with a goal of reducing recurrence (adjuvant treatment). Options for adjuvant treatment commonly include chemotherapy, and/or endocrine/hormonal therapy. Side effects from adjuvant treatment, especially chemotherapy, may cause significant morbidity and also reduce quality of life. Therefore, accurate identification of women who are at low risk of recurrence could avoid adjuvant treatment and associated side effects, without risking a preventable recurrence.

Risk factors for predicting breast cancer recurrence include lymph node involvement at time of primary diagnosis, larger tumor size, estrogen receptor negative status, higher histologic grade, higher nuclear grade, and overexpression of the HER2 protein. Online tools are available to assess the risks and benefits of additional therapies after surgery, including: the PREDICT Tool and Adjuvant! Online (AOL).

### Gene Expression Profiling

Breast cancer gene expression profiling (GEP) assays were developed to help predict the risk of local or distant breast cancer recurrence and response to treatment. The assays use various technologies (e.g., immunohistochemistry, quantitative reverse transcription polymerase chain reaction, microarray) to measure the expression levels of multiple genes in a tissue sample. Examples of available breast cancer prognostic GEP tests are as follows:

- BluePrint® (Agendia®)
- Breast Cancer Index<sup>SM</sup> (BCI), which combines the Molecular Grade Index (MGI) and the HOXB13:IL17BR Index (bioTheranostics, Inc.)
- BreastOncPx™ (LabCorp)
- BreastPRS™ (Signal Genetics)

- EndoPredict® (Myriad®)
- MammaPrint® (Agendia®)
- Mammostrat® (Clariant Diagnostic Services)
- Molecular Grade Index (AviaraDx, Inc.)
- Oncotype DX® Breast (Genomic Health Inc.)
- Oncotype DX® DCIS (Genomic Health Inc.)
- Prosigna™ (NanoString Technologies Inc.)
- TargetPrint® (Agendia®)
- Theralink® Reverse Phase Protein Array (RPPA) (Theralink® Technologies, Inc)

If these assays are more accurate at predicting disease recurrence or response to therapy than conventional methods, then patients with lower risk status may be able to safely avoid the side effects of adjuvant treatment.

## CLINICAL EVIDENCE AND LITERATURE REVIEW

### EVIDENCE REVIEW

#### Clinical Utility of Genetic Testing

Establishing the clinical utility of any test is a key component in determining its ultimate usefulness. In general, clinical utility may be established when published evidence demonstrates test results can be used to guide treatment, management, or preventive decisions; and those decisions lead to improved primary health outcomes. The proposed clinical utility of gene expression profile (GEP) tests varies depending on the clinical context. In the context of providing important information to guide decisions on adjuvant chemotherapy treatment decisions in patients with primary breast cancer, clinical utility studies of GEP tests report the following:

1. Long-term (10-year) data on estimated outcomes (e.g., recurrence or metastasis risk, distant-recurrence-free-interval probabilities) based on test scores; and
2. If test results led to changes (not predicted changes) in patient management; and
3. If test results led to improvements in clinically measurable patient outcomes patient (e.g., survival or mortality).

Numerous tests now have demonstrable clinical utility, and are recommended by clinical practice guidelines that are based on evidence. Many of the commercially available GEP tests for breast cancer prognosis only assess clinical validity compared to another type of GEP test. This is not considered an adequate surrogate for clinical utility, as the performance of one test compared to another does not establish the use of that test in treatment decisions and improve overall health outcomes. The following literature summary is predominantly focused on indications for breast cancer prognostic gene tests that do not yet have sufficient evidence of clinical utility.

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the clinical utility of gene expression profile (GEP) assays for management of breast cancer. Below is a summary of the available evidence identified through April of 2021.

#### BluePrint® (Agendia®)

## Description

BluePrint was developed to provide an additional method for the molecular subclassification of breast cancer. BluePrint functional molecular subtyping determines the mRNA levels of 80 genes that are proposed for discrimination between Luminal-type, HER2-type, and Basal-type tumors, each with marked differences in long-term outcome and response to neoadjuvant chemotherapy.<sup>3</sup>

## Nonrandomized Studies

In 2013, Glück et al. published a large retrospective analysis of 437 patients with early stage breast cancer from four trials to evaluate the prognostic ability of BluePrint /MammaPrint molecular subtyping versus clinical subtyping using immunohistochemistry/fluorescence in situ hybridization (IHC/FISH) for the determination of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2 status, and the impact of these subtyping assays on pathologic complete response (pCR) rate after neoadjuvant chemotherapy and long-term outcome (distant metastases-free survival [DMFS]).<sup>4</sup> The investigators reported that 43 of 107 (40%) HER2-positive patients were classified as Luminal-type B by BluePrint and, as a result, were predicted to have lower response rates to targeted therapy. When BluePrint was used in conjunction with MammaPrint, 90 of 435 (21%) patients were predicted to have excellent survival, 93% DMFS at five years, based on their classifications by the two tests in combination (Luminal A-type by BluePrint and low risk by MammaPrint). The addition of the MammaPrint score was reported to enable subdivision of the Luminal group into two types, Luminal A and B, which cannot be achieved with standard pathology. The pCR rate, which is thought to be a surrogate for long-term survival, did not provide any significant prognostic information for any of the BluePrint sub-type classifications. This analysis was not prospective and was performed on data from trials involving different institutions, chemotherapy regimens and definitions of pCR. Additional studies which report long-term data and whether the use of BluePrint subtyping leads to actual changes in patient management are needed.

In 2016, Viale et al. published results of an analysis of a case series that evaluated patient outcomes when traditional immunohistochemical pathological subtyping (PS) (ER, PgR, HER2 and Ki67) was compared to molecular subtyping using BluePrint, including 5806 patients from the MINDACT trial cohort.<sup>5</sup> Luminal cancers classified as HER-2+ using traditional subtyping had distant-metastasis-free survival (DMFS) estimates of 96%, similar to both subtypes of cancers determined by using BluePrint (Basal-type and Luminal type) (HR = 1.40, 95% CI 0.75-2.60; p = 0.294). However, when MammaPrint was used in conjunction with BluePrint and further classification of the Luminal subtypes was performed, more patients were identified with lower-risk Luminal A disease (63%) as compared with traditional subtyping (47%) with comparable five-year DMFS (≥96.0%). In addition, the use of BluePrint and MammaPrint combined led to re-stratification of 54% of patients with a Luminal-B subtype as found by traditional subtyping to a low-risk Luminal A-type group with comparable survival outcomes.

## **Breast Cancer Index<sup>SM</sup> (bioTheranostics, Inc.)**

### Description

The Breast Cancer Index (BCI) Risk of Recurrence & Extended Endocrine Benefit Test is a gene- GEP test for use in patients with estrogen receptor-positive (ER+), lymph node-negative (LN-), or lymph node

positive (LN+) early-stage invasive breast cancer, who are distant recurrence (DR)-free.<sup>6</sup> The BCI Predictive component of the assay reports whether a patient has a high or low likelihood of benefiting from extended (>5 years) endocrine therapy. The BCI Prognostic score stratifies patients as having low, intermediate, or high risk of overall (0- to 10-year) DR (metastatic), and as having low or high risk of late (5- to 10-year) DR. The test may be used at the time of diagnosis or following endocrine therapy.

### Nonrandomized Studies

In 2015, Sanft et al. published a prospective case series that assessed the impact of BCI results on physicians' recommendations for extended adjuvant endocrine therapy, including 96 patients with ER-positive stage I - III breast cancer who had completed at least 3.5 years of adjuvant endocrine therapy.<sup>7</sup> The investigators reported a 26% change in treatment recommendations after considering BCI results, with a significant decrease in recommendations for extended endocrine therapy from 74% to 54% ( $p=0.0003$ ). However, it was unclear if it was the prognostic and/or predictive component of the test that drove these changes. The study did not provide data on actual treatment decisions or long-term patient outcomes (e.g., morbidity and mortality) as a result of treatment decisions that were informed by BCI test results. Other limitations include the fact that it was unclear which version of the BCI test was used and the study reported different cutoffs than the commercially available version.

The BCI test has been reported to affect patient management decisions and is recommended by the NCCN for predictive and prognostic management.

### **EndoPredict® (Myriad®)**

#### Description

EndoPredict® detects the likelihood of late metastases (i.e., metastasis formation after more than five years) and can therefore guide treatment decisions for chemotherapy as well as extended anti-hormonal therapy.<sup>8</sup> EndoPredict® is a real-time, reverse transcription PCR (RT-PCR) assay of RNA isolated from tumor tissue samples that are either from a formalin-fixed paraffin-embedded (FFPE) block or a core needle biopsy that analyzes the expression of eight disease relevant genes (plus four reference genes) and reports an EP score. When the EP score is combined with tumor size and nodal status, it is reported as the EPclin score, which is proposed for evaluation of distant recurrence risk within 10 years of testing and to predict the benefit of chemotherapy.

### Nonrandomized Studies

In 2013, Müller et al. published a study that retrospectively evaluated the impact of the EndoPredict assay on treatment decisions for patients with breast cancer by way of a two-question questionnaire.<sup>9</sup> Of the 167 patients that underwent the EndoPredict test within a year, treatment information was only available for 130 patients (77.8%). The authors reported a change of therapy in a total of 37.7% of patients based on the results of the EndoPredict assay. Sixteen patients (12.3%) were recommended to undergo additional adjuvant chemotherapy, while 33 patients (25.4%) were switched from combination therapy to endocrine therapy alone. However, in the majority of patients (56.2%,  $n=73$ ) no change in therapy resulted from the EndoPredict assay results. However, neither adherence to therapy decisions nor actual patient outcomes that resulted from treatment changes were reported.



Large ongoing studies aim to prospectively evaluate therapy changes and additional clinical utility of this test, though it is recommended by the NCCN.

## **MammaPrint® (Agendia®)**

### Description

The MammaPrint 70-Gene Breast Cancer Recurrence Assay is performed by isolating tumor RNA which runs on a diagnostic microarray to determine gene expression of the 70 genes on the array.<sup>10</sup> A MammaPrint index is calculated using an algorithm that determines the molecular prognosis (high versus low risk of recurrence). A good prognosis signature is indicated if the correlation coefficient of a woman's tumor gene expression profile compared to the average profile of expression in those with a good-prognosis signature is greater than 0.4 (corresponding to a 10% false-negative rate). If those standards are not met, then the patient is determined to have a poor prognosis signature. A good prognosis signature is further defined as the probability of > 90% for 5-year distant metastasis-free survival (DMFS). Mammprint is recommended by the NCCN for specific patient populations.

### Nonrandomized Studies

In 2015, Kuijer et al. published evaluated the use of MammaPrint to guide AST decisions, using data from a Dutch registry of 2043 women with ER-positive, HER2-negative invasive breast cancer.<sup>11</sup> Of the 2043 women enrolled in the registry, 298 (14.6%) underwent testing with MammaPrint. The authors reported that the inclusion of MammaPrint results led to a significant reduction in the administration of adjuvant chemotherapy (9.5-9.9%, depending on the statistical model).

In 2016, Cardoso et al. published the first results from the Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy (MINDACT) study, a prospective phase 3 study evaluating the clinical utility of adding MammaPrint to standard clinical-pathological criteria using a modified version of the AOL tool in selecting patients for adjuvant chemotherapy.<sup>12</sup> This trial enrolled 6,693 women with early-stage breast cancer. Women identified as high clinical/high genomic risk were advised to undergo chemotherapy. Women identified as low clinical/low genomic risk were advised not to undergo chemotherapy. Women with discordant results (high clinical risk/low genomic risk [n=1550] or low clinical risk/high genomic risk [n=592]) were randomly assigned to the chemotherapy group or the no-chemotherapy group on the basis of either the clinical result or the genomic result. Of the women with low clinical risk/high genomic risk, there was no benefit from the use of adjuvant chemotherapy, as there was no difference in five- year, disease-free or overall survival rates between those who received chemotherapy and those who did not (five-year rate of survival without distant metastasis of 95 - 95.8% in both treatment groups). This finding indicates that there is no advantage of directing therapy on the basis of genomic risk among patients at low clinical risk. Of the women with high clinical risk/low genomic risk, the 5-year survival rate without distant metastasis was not significantly different among those who did not receive chemotherapy compared to those who did (94.4% versus 95.9%, respectively). In addition, subgroup analyses of women with up to three positive nodes yielded rates of survival without distant metastases were 95.6% in those who did not receive chemotherapy versus 96.3% in those who did. In node-negative women, rates of survival without distant metastases were 93.2% in those who did not receive chemotherapy versus 95.7% in those who did. Therefore, additional benefit of adjuvant chemotherapy may be small in both sub-groups. The investigators reported that among women with early-stage breast cancer who were at high clinical risk

and low genomic risk for recurrence (as determined by the assay), the receipt of no chemotherapy led to a 5-year rate of survival without distant metastasis that was 1.5 percentage points lower than the rate with chemotherapy. The authors concluded that the use of the 70-gene signature to guide chemotherapy treatment might lead to a reduction in the use of adjuvant chemotherapy in 46% of patients at high clinical risk.

### **Oncotype DX® Breast (Genomic Health Inc.)**

#### Description

The Oncotype DX breast cancer assay is a reverse transcription PCR (RT-PCR)-based profiling test that measures the RNA gene expression pattern of 21 genes (16 linked to molecular pathways in cancer and 5 reference genes) from formalin-fixed, paraffin-embedded (FFPE) tumor tissue from a patient with invasive breast cancer.<sup>13</sup> A proprietary formula is used to calculate a Recurrence Score (RS) that quantifies recurrence and likelihood of benefit of chemotherapy. This test is intended to determine the recurrence risk of early-stage invasive breast cancer and predict disease response to chemotherapy. The intended benefit of Oncotype DX is to prevent women with breast cancer from being exposed unnecessarily to toxic effects of adjuvant chemotherapy if the therapy would not benefit them. The use of this test allows for more accurate predictions of the risk of recurrence and chemotherapy response, thereby giving physicians an additional prognostic tool to identify women with breast cancer who will benefit from adjuvant chemotherapy to decrease the risk of disease recurrence from those who would not. The NCCN recommends this test for specific populations.

#### Nonrandomized Studies

In 2011, Oratz et al. published a retrospective analysis of 160 node-positive patients to determine whether results from the Oncotype DX breast cancer assay affected adjuvant treatment recommendations.<sup>14</sup> In the low RS (low risk group) 60% of patients had a treatment change recommendation based on their RS score, 49% of which were recommended to only undergo endocrine therapy and not chemotherapy. However, in the intermediate RS score group the impact on the test was less convincing, where 38% (20/53) of patients deemed intermediate risk had a change in treatment recommendation. In the intermediate RS group, 21% were recommended to decrease the intensity of their treatment (switch to endocrine therapy only) and 12% were recommended to increase their therapy and include chemotherapy. This study had a number of additional limitations, including a low patient response rate (16%), incomplete patient characteristic data provided in the publication, it was unclear if the reason for change in treatment was based on patient preference or RS result, and no statistical analyses were reported.

In 2015 Bargallo et al. published a prospective study which assessed this impact of Oncotype DX in decision making in 96 patients, 34 of whom were node-positive.<sup>15</sup> In these patients, 41% (14/34 patients) received changes in treatment recommendations after receiving the assay results. All the patients that received treatment recommendation changes had RS scores in the low to low-intermediate range. Six percent of node-positive women (n=2) were recommended to add chemotherapy to their hormonal treatment, and 32% were recommended to remove chemotherapy from their combination treatment. Similar results have been reported by other small prospective studies that have included and separately analyzed node-positive women.<sup>16-18</sup> These previously published studies included from 20-120 node-positive patients but did not report if changes in treatment recommendations improved actual patient outcomes.

In 2017, Stemmer et al. published two retrospective analyses of treatments and clinical outcomes of subjects, both node-negative and node-positive, who were treated according to Oncotype RS scores. The node-negative study included 1801 subjects, while the node-positive analysis included 709 subjects.<sup>19,20</sup> The five-year distant recurrence rates were substantially higher in the node-positive subjects (RS < 18 = 3.2%, RS 18–30 = 6.3% and RS ≥ 31 = 16.9%) than the node-negative subjects (RS < 18 = 0.8%, RS 18–30 = 3.0% and RS ≥ 31 = 8.6%) for all three RS score groups. In the node-positive subjects stratified by nodal status, five-year distant recurrence rates were 1.2% for subjects with N1mi, 4.4 for those with one positive node, and 5.4% for 2-3 positive nodes. The five-year breast cancer-related death was also higher in the node-positive subjects in both RS groups assessed (RS < 18 = 0.5%, RS 18–30 = 3.4% and RS ≥ 31 = 5.7%) than the node-negative subjects (RS < 18 = 0.0%, RS 18–30 = 0.9% and RS ≥ 31 = 6.2%). In the endocrine therapy only subjects, the five-year distant recurrence rates were also higher in the node-positive subjects (RS 18–30 = 2.7% and RS ≥ 31 = 9.9%) compared to the node-negative subjects (RS 18–30 = 2.0% and RS ≥ 31 = 5.8%).

### **Oncotype DX® DCIS (Genomic Health Inc.)**

#### Description

The Oncotype DX DCIS breast cancer assay analyzes the expression profile of a subset of the 21-gene Oncotype DX® breast assay described above, and is proposed for patients diagnosed with noninvasive ductal carcinoma in situ (DCIS).<sup>21</sup> Expression levels from 12 genes (7 cancer related and 5 reference genes) are incorporated into a proprietary algorithm to calculate a DCIS Score, which proposes to quantify (1) the likelihood of local recurrence (DCIS or invasive carcinoma) at 10 years; and (2) predict the risk of an invasive carcinoma local event at 10 years to help inform the treatment plan.

#### Nonrandomized Studies

In 2015, Alvarado et al., 2015 published the results of a multicenter prospective case series that assessed whether Oncotype DX impacted physicians' recommendations regarding radiation therapy for 122 ductal carcinoma in situ (DCIS) patients.<sup>22</sup> The study reported a 31.1% change in radiation therapy recommendations based on the test result. The change in treatment recommendation was statistically significant ( $p=0.008$ ). Assessment of whether or not the DCIS Score resulted in an actual change in patient management was not addressed in the study.

In 2017, Manders et al. published the results of a prospective multi-site case series aimed determining the impact of the results of the 12-gene Oncotype DCIS Score assay on radiotherapy recommendations for 127 patients with pure ductal carcinoma in situ (DCIS) following breast-conserving surgery.<sup>23</sup> Overall, the results of the DCIS assay altered treatment recommendations by 26.4 % (30.4% by surgeons and 22.0 % of recommendations by radiation oncologists. Recommendations for radiotherapy increased for the intermediate and high DCIS score groups, and decreased for the low-risk groups. Among patients with confirmed completed questionnaires ( $n = 32$ ), decision conflict ( $p = 0.004$ ) and state anxiety ( $p = 0.042$ ) decreased significantly from pre- to post-assay. Neither adherence to therapy decisions nor actual patient outcomes, based on recommended treatment changes, were reported in this study.

### **Prosigna™ Breast Cancer Prognostic Gene Signature Assay (NanoString Technologies Inc.)**

## Description

Prosigna is an assay that integrates expression data from the PAM50 assay (which is a 50-gene expression assay) with clinical variables to generate a Risk of Recurrence (ROR) score. The ROR score is offered to predict the probability of distant recurrence-free survival (DRFS) at 10 years for endocrine-treated hormone receptor–positive (HR+) breast cancer patients. The Prosigna assay uses NanoString’s proprietary nCounter Dx Analysis System to analyze breast cancer gene expression and is performed using messenger RNA (mRNA) isolated from formalin-fixed paraffin-embedded (FFPE) breast tumor specimens or tissue slides. The Prosigna test currently available in the United States—which does not include the determination of intrinsic subtypes—derives the Prosigna ROR score from 46-gene expression of the original PAM50, 50-gene expression classifier. The test is 510(k) cleared by the FDA and recommended by the NCCN for specific patient populations.

## **Studies Comparing GEP Tests**

A large number of recent studies have been published with direct comparisons of the clinical validity of two or more GEPs for breast cancer. However, studies comparing these tests do not confer direct clinical utility. Several of the more recent studies are summarized below.

## Systematic Reviews

In 2017, Blok et al. published the results of a European systematic review that assessed the clinical utility of MammaPrint, OncotypeDX, PAM50/Prosigna and Endopredict assays, including 28 studies (22 for OncotypeDX, 4 for MammaPrint, and 1 for both Prosigna and Endopredict).<sup>24</sup> The reviewers reported that in a pooled analysis, the decrease in chemotherapy based on assay results was the most pronounced for OncotypeDX (45.7% from chemotherapy to endocrine therapy alone or no adjuvant therapy) compared to MammaPrint (32.2% decrease). However, these pooled results should be interpreted with caution, since there was substantial heterogeneity in the number of studies per assay, the baseline patient populations, and study designs. Similar results were reported by a second systematic review published in 2017 by Scope et al., which evaluated the clinical utility of Oncotype Dx, MammaPrint and MammoStrat, finding Oncotype to be the most robust assay.

## Nonrandomized Studies

The first study comparing multi-gene expression assays for breast cancer was published by Varga et al. in 2013.<sup>25</sup> Breast cancer samples from 34 patients (n=21 node-negative, 62%) were retrospectively analyzed using the EndoPredict® test after being analyzed previously using Oncotype DX® Breast. The EndoPredict® EP score classified 11 patients as low-risk and 23 patients as high-risk, whereas the Oncotype DX® Breast RS Score defined 15 patients as low-risk, 19 patients as intermediate-high risk (combined group). There were major discrepancies between the two tests in six of 34 patients (18%). The authors reported moderate concordance of classification (76%) and moderate but significant correlation (0.65; p<0.01) between the RS and EP test scores. However, when EP scores are combined with tumor size and nodal status to generate EPclin scores and then compared to RS scores, concordance and correlation between scores decreased (65% and 0.45, respectively). The authors concluded that further studies were needed to compare both tests with regard to prediction of distant metastasis, chemotherapy benefit and health outcomes.

More recently, in 2016, Buus et al., published a study comparing the prognostic ability of EndoPredict® scores with Oncotype DX® RS scores for early (0-5 years) and late (5-10 years) distant recurrence (DR)

risk.<sup>26</sup> This study included 928 (n=680 node-negative, 73%) hormone receptor-positive, HER2-negative tumor samples from patients previously recruited for the TransATAC trial. EPclin scores identified 58.8% of patients as low risk, whereas RS scores identified 61.7% patients as low risk. In multivariate analyses, both EP and EPclin scores provided significantly more prognostic information than RS scores for both early and late DR as well as all DR (0-10 years), with similar results observed within node-negative and -positive subgroups. The hazard ratio between the high+medium-risk (combined for RS scores for comparison to EP scores) vs low-risk groups was marginally greater for EP (HR = 2.98) and substantially greater for EPclin (HR = 5.99) than for RS (HR = 2.73.001).

Also in 2016, Martin et al. compared the prognostic ability of EndoPredict EP scores to the PAM50 risk of recurrence (ROR) scores in node-positive, estrogen receptor-positive, and HER2-negative breast cancer in 536 patients recruited for the GEICAM/9906 trial, who were receiving adjuvant chemotherapy followed by endocrine therapy (ET).<sup>27</sup> However, both the EndoPredict and PAM-50 tests have only been validated on cohorts receiving hormone therapy alone. EPclin and two different ROR scores: ROR-S (based on tumor subtype) and ROR-P (based on subtype and tumor size) were compared for their prognostic performance. Ten-year metastasis-free survival in groups with low-risk scores were similar between tests (ROR-S 87 %; ROR-P 89 %; EP 93 %). The authors concluded that, despite the fact that there is limited overlap of genes assayed for each test; both PAM-50 ROR and EndoPredict EP scores can reliably predict risk of distant metastasis in node-positive ER+/HER2-negative patients treated with chemotherapy and ET. For both tests, the addition of clinical parameters into risk scores improves their prognostic ability for both tests used.

A recent comprehensive analysis of the GEP assays as a prognostic tool for distant recurrence in estrogen receptor-positive, *ERBB2*-negative early-stage breast cancer was published by Sestak et al. in 2018.<sup>28</sup> In a retrospective cohort, the authors reported a preplanned secondary analysis of a randomized controlled trial that included within-patient biomarker analysis of 6 multigene signatures in 774 postmenopausal women with ER-positive *ERBB2* (formerly HER2)-negative breast cancer. The signatures included the Oncotype Dx recurrence score (RS), PAM50-based Prosigna risk of recurrence (ROR), Breast Cancer Index (BCI), EndoPredict (EPclin), Clinical Treatment Score (CTS), and 4-marker immunohistochemical score (IHC4). Previously, individual assessments of the commercially available signatures were published, each having had significant and similar prognostic effects during the first 5 years after diagnosis. The updated analyses offered difference in prognostic performance during 10 years of follow-up. BCI was among the tests having more prognostic significance for late recurrence (5 to 10 years) when compared with IHC4 and RS. Independent prognostic information was stratified by both recurrence risk in years of follow-up (overall 0 to 10 and 5 to 10) and node status (node-negative disease and 1 to 3). Five hundred ninety-one women (of 774) had node-negative disease; 227 were node-positive. For 0 to 10 years, BCI was statistically significantly more prognostic than other signatures, though less so for node-positive disease than node-negative, hazard ratios (HRs), of 2.46; 95% CI, 1.88-3.23 and 1.67 (1.21-2.29), respectively. For late-recurrence (5 to 10 years), in node-negative women BCI provided significant prognostic value (HR, 2.30; 95% CI, 1.61-3.30) and substantially more than CTS alone (HR, 1.95; 95% CI, 1.43-2.65). In the node-positive population, BCI had more prognostic value than IHC4 and RS (HR, 1.60 CI, 1.04-2.47), but less so than CTS, ROR, and EPclin. Overall, for late distance recurrence, the authors reported that BCI, ROR, and EPclin provided independent prognostic value for women with node-negative disease and those with 1 to 3 positive nodes. Limitations of this study include authors having affiliations or employment with manufacturers of these test. There were multiple tests and manufacturers included in the study.

## Other GEP Assays

There are additional gene expression profiling assays on the market that lack published evidence regarding their clinical utility for patients with breast cancer; these include BreastOncPX™, BreastPRS™, Mammostrat®, Molecular Grade Index, TargetPrint® and Theralink® Reverse Phase Protein Array (RPPA).

## CLINICAL PRACTICE GUIDELINES

### National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines on breast cancer (v4.2023) recommend multigene assays for consideration of addition of adjuvant systemic chemotherapy to adjuvant endocrine therapy.<sup>29</sup> Oncotype DX®, MammaPrint®, Prosigna™ (PAM50), EndoPredict®, and Breast Cancer Index<sup>SM</sup> (BCI) gene expression profiling tests are listed as being prognostic.

The 21-gene Oncotype DX® assay is preferred by the NCCN Breast Cancer Panel for prognosis and prediction of chemotherapy benefit. Other prognostic gene expression assays can provide prognostic information, but the ability to predict chemotherapy benefit is unknown.

The Breast Cancer Index<sup>SM</sup> (BCI) assay is predictive of benefit of extended adjuvant endocrine therapy.

Each of these tests has specific populations identified, along with the NCCN category of evidence and consensus.

### American Society of Clinical Oncology

In 2016, ASCO published evidence-based clinical practice guidelines on the use of biomarkers to guide decisions regarding adjuvant systemic therapy for women with early-stage invasive breast cancer.<sup>30</sup> Subsequently, in 2017, ASCO published a focused update which addressed the use of the MammaPrint assay.<sup>31</sup> Below is a summary of the recommendations provided by the ASCO guideline on the GEP assays addressed in this policy for ER/PgR-positive, HER2-negative breast cancer:

Test	Recommendation	Type	Evidence Quality	Recommendation Strength
Node-negative				
<b>Breast Cancer Index (BCI)</b>	May use the Breast Cancer Index to guide decisions on adjuvant systemic therapy.	Evidence-based	Intermediate	Moderate
<b>EndoPredict</b>	May use the 12-gene risk score (EndoPredict) to guide decisions on adjuvant systemic chemotherapy.	Evidence-based	Intermediate	Moderate
<b>MammaPrint</b>	<ul style="list-style-type: none"> <li>The MammaPrint assay may be used in those with high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy.</li> <li>The MammaPrint assay should not be used in those with low clinical</li> </ul>	Evidence-based	High	Strong

	risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy.			
<b>Oncotype DX Breast</b>	May use the 21-gene recurrence score (RS; Oncotype DX; Genomic Health) to guide decisions on adjuvant systemic chemotherapy.	Evidence-based	High	Strong
<b>PAM50/Prosigna</b>	May use the PAM50 risk of recurrence (ROR) score (Prosigna), in conjunction with other clinicopathologic variables, to guide decisions on adjuvant systemic therapy.	Evidence-based	High	Strong
<b>Node-positive</b>				
<b>MammaPrint</b>	<ul style="list-style-type: none"> <li>The MammaPrint assay may be used in those with high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy.</li> </ul>	Evidence-based	High	Moderate

The ASCO guidelines defined clinical utility as “if use of the test is associated with a favorable balance of benefits to harm compared with treatment of the patient in the absence of the biomarker test result”. Based on this relatively liberal definition, ASCO only recommends three assays with the highest confidence (and ONLY in node-negative patients): Oncotype DX Breast, Prosigna and now MammaPrint. While the recommendations for Oncotype DX Breast and Prosigna were based on multiple high quality studies with 10-year follow-up, the MammaPrint recommendation was based solely on one publication reporting five-year trial outcomes.

Moderate strength recommendations for the use of the Breast Cancer Index, EndoPredict and MammaPrint assays in node-negative women reflects the panel’s concerns regarding the quality of the studies published on the clinical utility of these tests and the overall consistency of the results between studies. Of note, the updated recommendation for the use of MammaPrint was based primarily on the five-year results of the MINDACT study published in 2016 which indicated that the assay may be of use in subjects with high but not low clinical risk.<sup>12</sup>

With the exception of the MammaPrint assay in patients of with high clinical risk (moderate strength recommendation), the panel recommended against the use of GEP assays in node-positive women based on the fact that women with positive nodal status in general have much higher odds of distant recurrence than node-negative women, regardless of whether a GEP test has determined them to be at low-risk of recurrence. The panel believes that the number of node-positive women “who will benefit from the adjuvant chemotherapy will far exceed the number who will be harmed.” In addition, ASCO found no studies on the clinical utility for the use of any of the GEPs assays in node-positive women. However, in 2017, ASCO updated their stance on the MammaPrint assay, recommending the following:

**Node-negative:** “If a patient has hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-negative breast cancer, the MammaPrint assay may be used in those with high clinical risk to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good-prognosis population with potentially limited chemotherapy benefit. Women in the low clinical risk category did not benefit from chemotherapy regardless of genomic MammaPrint risk group. Therefore, the MammaPrint assay does not have clinical utility in such patients.”

Node-positive: “If a patient has hormone receptor-positive, HER2-negative, node-positive breast cancer, the MammaPrint assay may be used in patients with one to three positive nodes and a high clinical risk to inform decisions on withholding adjuvant systemic chemotherapy. However, such patients should be informed that a benefit from chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node.”

## EVIDENCE SUMMARY

### **Oncotype DX® Breast (RS), MammaPrint®, Prosigna™ (PAM50), EndoPredict® or Breast Cancer Index<sup>SM</sup> (BCI)**

There is enough research to show that the use of Oncotype DX® Breast (RS), MammaPrint®, Prosigna™ (PAM50), EndoPredict® or Breast Cancer Index<sup>SM</sup> (BCI) gene expression profiling tests may improve overall health outcomes when testing is used to guide treatment decisions in highly selective patients with primary breast cancer. Overall health outcomes have been shown to improve for some hormone receptor positive, HER-2 negative individuals whose providers used prognostic and therapy-predictive assays to help guide treatment decisions. Clinical practice guidelines based on research also recommend that select patients be considered for prognostic and therapy-predictive assays including Oncotype DX® Breast (RS), MammaPrint®, Prosigna™ (PAM50), EndoPredict® or Breast Cancer Index<sup>SM</sup> (BCI) gene expression profiling tests. Therefore, the use of Oncotype DX® Breast (RS), MammaPrint®, Prosigna™ (PAM50), EndoPredict® or Breast Cancer Index<sup>SM</sup> (BCI) gene expression profiling tests may be considered medically necessary and covered when policy criteria are met. When policy criteria are not met, testing with the Oncotype DX® Breast (RS), MammaPrint®, Prosigna™ (PAM50), EndoPredict® or Breast Cancer Index<sup>SM</sup> (BCI) tests is considered not medically necessary.

### **Other GEP Assays for Breast Cancer**

There is not enough research to show that other breast cancer prognostic and therapy-predictive assays improve overall health outcomes when used to guide breast cancer treatment decisions. Other assays include but are not limited to BreastOncPXTM, BreastPRSTM, Mammostrat®, Molecular Grade Index, and TargetPrint®. Although some of these tests may show promise in early research, the impact on long-term health outcomes has not been proven. In addition, current clinical practice guidelines do not strongly recommend the use of any of the above mentioned assays. Therefore, breast cancer prognostic and therapy-predictive assays not listed in policy criteria above, including but not limited to BreastOncPXTM, BreastPRSTM, Mammostrat®, Molecular Grade Index, TargetPrint® and Theralink® Reverse Phase Protein Array (RPPA) are considered not medically necessary.

## **BILLING GUIDELINES AND CODING**

Both 81521 and 81523 may not be billed together for testing on the same tumor. If one test was billed, the other will be considered not medically necessary and not covered.

HCPCS code S3854 is not recognized as a valid code for claim submission as indicated in the relevant Company Coding Policy (*HCPCS S-Codes and H-Codes*, 22.0). Providers need to use alternate available CPT or HCPCS codes to report for this service. If no specific CPT or HCPCS code is available, then an unlisted code may be used. Note that unlisted codes are reviewed for medical necessity, correct coding,



and pricing at the claim level. Thus, if an unlisted code is billed related to a non-covered service addressed in this policy, it will be denied as not covered.

CODES*		
CPT	0009U	Oncology (breast cancer), ERBB2 (HER2) copy number by FISH, tumor cells from formalin-fixed paraffin-embedded tissue isolated using image-based dielectrophoresis (DEP) sorting, reported as ERBB2 gene amplified or non-amplified
	0045U	Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score
	0153U	Oncology (breast), mRNA, gene expression profiling by next-generation sequencing of 101 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a triple negative breast cancer clinical subtype(s) with information on immune cell involvement
	0249U	Oncology (breast), semiquantitative analysis of 32 phosphoproteins and protein analytes, includes laser capture microdissection, with algorithmic analysis and interpretative report
	0295U	Oncology (breast ductal carcinoma in situ), protein expression profiling by immunohistochemistry of 7 proteins (COX2, FOXA1, HER2, Ki-67, p16, PR, SIAH2), with 4 clinicopathologic factors (size, age, margin status, palpability), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a recurrence risk score
	81479	Unlisted molecular pathology procedure
	81518	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy
	81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score
	81520	Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score ( <i>Prior-authorization effective 3/1/2018</i> )
	81521	Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis
	81522	Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score
	81523	Oncology (breast), mRNA, next-generation sequencing gene expression profiling of 70 content genes and 31 housekeeping genes, utilizing formalin-

		fixed paraffin-embedded tissue, algorithm reported as index related to risk to distant metastasis
	81599	Unlisted multi-analyte with algorithmic analysis
	84999	Unlisted chemistry procedure
	S3854	Gene expression profiling panel for use in the management of breast cancer treatment
<b>HCPCS</b>	None	

**\*Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- See the non-covered and prior authorization lists on the Company [Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website](#) for additional information.
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as “medically unlikely edits” (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

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## POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
7/2023	Annual Review. Updated investigational criteria to not medically necessary.
8/2023	Interim Review. Code moved to policy. No configuration changes.
10/2023	Interim Review. Code moved from policy. No configuration changes.