GUIDELINES
This policy does not certify benefits or authorization of benefits, which is designated by each individual policyholder contract. Paramount applies coding edits to all medical claims through coding logic software to evaluate the accuracy and adherence to accepted national standards. This guideline is solely for explaining correct procedure reporting and does not imply coverage and reimbursement.

DESCRIPTION
Clinical evidence has demonstrated that among individuals with breast cancer there is a continuum of disease recurrence risk, based on many factors including age, the presence of various hormone receptors in tumor samples, tumor size, whether or not the cancer has spread outside the breast, and others. Clinicians have, for practical use, divided this continuum up into three risk categories: (1) low-risk, (2) intermediate-risk, and (3) high-risk. These risk categories have been used as a method of helping to determine what treatment methods to use for specific individuals. In individuals deemed at high-risk for disease recurrence, the medical evidence has shown that the use of chemotherapy in addition to other treatment may provide a significant survival benefit. In low-risk individuals, the data has shown that chemotherapy in addition to other treatment does not provide any significant benefits. However, the available information regarding whether or not intermediate-risk individuals benefit from chemotherapy is unclear. Traditionally, treating clinicians have to balance each individual’s risk of disease recurrence with the risks of chemotherapy, which include hair loss, nausea, vomiting, weakness, infection, and others.

Recently a new type of test, the gene expression profiling assay, has been developed to help clinicians determine which populations of intermediate-risk individuals would benefit from chemotherapy. Gene expression profiling assays measure the presence of a variety of genes which have been associated with the recurrence of breast cancer. Using these tests, in conjunction with other traditional risk assessment methods, clinicians may be able to more accurately determine which intermediate risk individuals would benefit from chemotherapy, and which individuals would not. In this way individuals most likely to benefit from chemotherapy are identified and receive needed care, and those individuals who would not benefit are spared the unnecessary treatment and risks associated with chemotherapy without adversely affecting disease-free and overall survival outcomes.

The Oncotype DX® breast cancer test, is a test that examines a breast cancer patient's tumor tissue at a molecular level, and gives information about a patient's individual disease. This information can help individualize breast cancer treatment planning and identify options. The Oncotype DX® breast cancer test is the only multigene expression test commercially available that has clinical evidence validating its ability to predict the likelihood of chemotherapy benefit as well as recurrence in early-stage breast cancer. The Oncotype DX® gene expression assay is intended to be used by women with early-stage (stage I or II), node-negative, estrogen receptor-positive (ER+) invasive breast cancer who will be treated with therapy.

MammaPrint® is a multigene expression test that evaluates a set of 70 genes involved in cell proliferation, invasion, metastasis, and angiogenesis, and provides a determination of high or low risk of distant metastasis. Although it appears to have prognostic validity for identifying women whose early-stage breast cancer is more likely to metastasize, it is not clear how much value MammaPrint adds to existing risk estimation techniques.

Prosigna Breast Cancer Prognostic Gene Signature Assay integrates expression data from the PAM50 assay, with clinical variables to generate a Risk of Recurrence (ROR) score to predict the probability of DRFS at 10 years for endocrine-treated HR+ breast cancer patients.

Breast Cancer IndexSM is a real-time reverse transcription PCR assay performed using formalin-fixed paraffin-embedded tissue. The test has 2 components: the BCI Prognostic (risk of recurrence) and BCI Predictive (likelihood of benefit). The Prognostic component combines 2 indexes to provide an individualized risk of late (5 to 10 years post-diagnosis) distant recurrence and risk of overall (0 to 10 years post-diagnosis) distant recurrence for breast cancer. The BCI Predictive component is based on the homeobox B13/interleukin 17 receptor B (HOXB13:IL17BR) (H/I) index and provides prediction of benefit from extended (> 5 years) endocrine therapy.

EndoPredict is a real-time, reverse transcription PCR assay of RNA isolated from tumor tissue samples that are either from a formalin-fixed paraffin-embedded block or a core needle biopsy that is used to calculate the EP score.
and the EPclin score to assess the risk of distant recurrence within 10 years of testing and to predict the benefit of chemotherapy.

HERmark® Breast Cancer Assay is used to help determine prognosis and therapeutic choices for metastatic breast cancer. HERmark testing has been proposed for a number of indications, including use to predict response to trastuzumab in the treatment of metastatic breast cancer.

The clinical utility of genetic expression assay in profiling of breast cancer tumors has not yet been established through large, well-designed prospective clinical trials except for Oncotype DX®, MammaPrint®, Prosigna Breast Cancer Prognostic Gene Signature Assay, Breast Cancer Index℠, and EndoPredict breast cancer tests. Comparisons of genetic expression assays to established algorithm tools are lacking in the published, peer-reviewed scientific literature. The impact on meaningful health outcomes in routine clinical practice remains unknown. Supporting data on the use of gene expression assays in men with breast cancer are also lacking. Further, consensus support by professional societies/organizations in the form of guidelines or recommendations is lacking in the published scientific literature. At this time the role of such assays has not yet been established.

**POLICY**

Prior authorization is required for all product lines:
- Oncotype DX® Breast Cancer Assay (81519)
- MammaPrint® (81521)
- Prosigna Breast Cancer Prognostic Gene Signature Assay (81520, 0008M)
- Breast Cancer Index℠ (81479)
- EndoPredict (81479, S3854) (Code S3854 is Non-Medicare.)

HERmark® Assay (81479) requires prior authorization for Elite. HERmark® Assay (81479) is non-covered for HMO, PPO, Individual Marketplace, & Advantage.

All other genetic expression assays for breast cancer prognosis are non-covered for all product lines (this list may not be all inclusive):
- BluePrint™ Molecular Subtyping Profile
- Breast Cancer Gene Expression Ratio (also known as Theros H/I℠)
- BreastNext™
- BreastOncPX™
- BreastPRS
- Combimatrix™ Breast Cancer Profile
- eXagen®
- Invasiveness Signature™
- Insight® DX Breast Cancer Profile
- Mammostrat™
- NexCourse® Breast IHC4
- NuvoSelect™ eRx 200-Gene Assay
- The Oncotype DX® Breast DCIS Score™ Test (0045U)
- PAM50 Breast Cancer Intrinsic Classifier™
- Randox Assay
- Rotterdam Signature 76-Panel
- SYMPHONY™ Genomic Breast Cancer Profile
- TargetPrint®
- TheraPrint™
- The 41-gene signature assay
- The 76-gene "Rotterdam signature" assay
- THEROS Breast Cancer Index℠

Paramount covers Oncotype DX® Breast Cancer Assay as medically necessary to assess the need for adjuvant chemotherapy in a woman with recently diagnosed breast cancer when ALL of the following criteria are met:
- Breast tumor is stage 1 or stage 2
- There is no evidence of distant metastatic breast cancer
- Breast tumor is estrogen-receptor positive
- Breast tumor is HER2-receptor negative
• Adjuvant chemotherapy (i.e., chemotherapy not precluded due to other factors) is being considered and this testing is being ordered specifically to guide decision making as to whether or not adjuvant chemotherapy should be utilized
• EITHER of the following criteria:
  o Axillary-node status is negative (micrometastasis is no greater than 2.0 millimeters) whether the woman is pre- or post-menopausal
  o Up to three positive axillary nodes in a post-menopausal woman

Paramount covers MammaPrint® breast cancer recurrence signature for predicting breast cancer recurrence when ALL of the following criteria are met:
• Breast cancer newly diagnosed in male or female
• Breast tumor is ER positive or ER negative
• Breast tumor is HER2 receptor negative, as determined by IHC orISHassay
• Breast tumor size greater than 0.5 cm but less than or equal to 2.0 cm
• Negative axillary lymph nodes (nonmetastatic) (pN0)
• Individual has been assessed (e.g., Adjuvant! Online) and determined to be a candidate for adjuvant chemotherapy (i.e., chemotherapy is not disallowed due to other factors, such as advanced age or comorbidities)
• Specimen submitted for analysis is fresh frozen tumor tissue

Paramount covers Prosigna Breast Cancer Prognostic Gene Signature Assay, Breast Cancer IndexSM, and EndoPredict to assess necessity of adjuvant chemotherapy in females or males with recently diagnosed breast tumors, where ALL of the following criteria are met:
• Breast cancer is nonmetastatic (node negative)
• Breast tumor is estrogen receptor positive
• Breast tumor is HER2 receptor negative
• Adjuvant chemotherapy is not precluded due to any other factor (e.g., advanced age and/or significant comorbidities)
• Member and physician (prior to testing) have discussed the potential results of the test and agree to use the results to guide therapy

Paramount does not cover Oncotype DX®, MammaPrint®, Prosigna Breast Cancer Prognostic Gene Signature Assay, Breast Cancer IndexSM, and EndoPredict breast cancer tests for ANY other clinical evaluation because it is considered experimental, investigational or unproven.

Paramount does not cover repeat testing of a breast cancer tumor using ANY assay of genetic expression because it is considered not medically necessary.

Paramount considers use of more than one type of test to determine necessity of adjuvant therapy in breast cancer (Oncotype DX®, MammaPrint®, Prosigna Breast Cancer Prognostic Gene Signature Assay, Breast Cancer IndexSM, and EndoPredict) experimental and investigational.

**HMO, PPO, Individual Marketplace, Advantage**
Gene expression profiling as a technique of managing the treatment of breast cancer is considered investigational and not medically necessary when a gene profiling test other than the Oncotype DX® Breast Cancer Assay, MammaPrint®, Prosigna Breast Cancer Prognostic Gene Signature Assay, Breast Cancer IndexSM, or EndoPredict is being used.

**Elite**
While there is insufficient evidence in the published medical literature to demonstrate the safety, efficacy and long-term outcomes for HERmark® Assay (81479) per CMS guidelines it may be covered with a prior authorization for Elite members.

**CODING/BILLING INFORMATION**
The appearance of a code in this section does not necessarily indicate coverage. Codes that are covered may have selection criteria that must be met. Payment for supplies may be included in payment for other services rendered.

<table>
<thead>
<tr>
<th>CPT CODES</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>81519</td>
<td>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</td>
</tr>
<tr>
<td>81520</td>
<td>Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing</td>
</tr>
</tbody>
</table>
formalin-fixed paraffin embedded tissue, algorithm reported as a recurrence risk score (Effective 01/01/2018)

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 (Effective 01/01/2018)

84999 Unlisted chemistry procedure

0008M Oncology (breast), mRNA analysis of 58 genes using hybrid capture, on formalin-fixed paraffin prognostic algorithm reported as a risk score (Deleted code effective 12/31/17)

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

HCPCS CODE
S3854 Gene expression profiling panel for use in the management of breast cancer treatment


REVISION HISTORY EXPLANATION
09/09/14: Policy created to reflect most current clinical evidence per Medical Policy Steering Committee.
10/22/15: Removed CPT codes 81599 & 84999 and added 81519 & 0008M to policy. Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).
03/25/16: Code 81519 is now covered with prior authorization per ODM guidelines. Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).
04/22/16: Deleted Code Effective 12/31/2015 S3854. Added code 84999. Prosigna Breast Cancer Prognostic Gene Signature Assay (0008M), HERmark® (81479) and Breast Cancer IndexSM (81479) are covered for Elite only per CMS guidelines. Added MammaPrint® (84999) as covered for all product lines. Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).
09/01/16: Clarified InterQual® criteria sets for Oncotype DX® breast cancer test only.
01/01/17: Code S3854 reinstated effective 01/01/17 with same description per HCPCS book.
08/25/17: Paramount does not utilize InterQual® criteria sets for Oncotype DX® Breast Cancer Assay. Prosigna Breast Cancer Prognostic Gene Signature Assay (0008M), Breast Cancer IndexSM (81479) & EndoPredict (81479, S3854) are now covered with prior authorization for all product lines. Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).
12/15/17: Added effective 01/01/2018 new codes 81520 (Prosigna) & 81521 (MammaPrint) as covered with prior authorization for all product lines. Effective 12/31/17 deleted code 0008M. Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).
07/26/18: Added effective 07/01/2018 new code 0045U (The Oncotype DX® Breast DCIS Score™ Test) & as non-covered for all product lines. FoundationOne™ removed from policy. Refer to PG0438 Next Generation Sequencing (NGS) Tests for Advanced Cancer for coverage determination of FoundationOne CDx™ (F1CDx). Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).

REFERENCES/RESOURCES
Centers for Medicare and Medicaid Services, CMS Manual System and other CMS publications and services
Ohio Department of Medicaid http://jfs.ohio.gov/
American Medical Association, Current Procedural Terminology (CPT®) and associated publications and services
Centers for Medicare and Medicaid Services, Healthcare Common Procedure Coding System, HCPCS Release and Code Sets
Industry Standard Review
Hayes, Inc.