Important Information – Please Read Before Using This Policy

These services may or may not be covered by all Medica plans. Please refer to the member’s plan document for specific coverage information. If there is a difference between this general information and the member’s plan document, the member’s plan document will be used to determine coverage. With respect to Medicare and Minnesota Health Care Programs, this policy will apply unless those programs require different coverage. Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions about this Medica coverage policy may call the Medica Provider Service Center toll-free at 1-800-458-5512.

Medica coverage policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care and treatment.

Coverage Policy
Oncotype DX® Breast Cancer Assay is COVERED for patients with recently diagnosed breast cancer when all of the following criteria are met:
1. The tumor is stage I or stage II
2. The tumor is estrogen receptor and/or progesterone receptor positive
3. The tumor is HER2-receptor negative
4. The individual is axillary-node negative, with or without axillary-node micrometastasis 2.0 millimeters or less in size in one or more lymph nodes, or has one to three positive ipsilateral axillary lymph nodes
5. The individual is a candidate for hormone therapy (e.g., tamoxifen or aromatase inhibitors) and adjuvant chemotherapy, and the results will guide whether or not to undergo adjuvant chemotherapy.

Oncotype DX Breast Cancer Assay is investigative and unproven and therefore NOT COVERED for all other clinical presentations and conditions. There is insufficient reliable evidence in the form of high quality peer-reviewed medical literature to establish the efficacy or effects on health care outcomes.

Breast Cancer Index™, EndoPredict®, MammaPrint®, and Prosigna™ Gene Signature are COVERED for patients with recently diagnosed breast cancer when all of the following criteria are met:
1. The tumor is stage I or stage II
2. The tumor is estrogen receptor and/or progesterone receptor positive
3. The tumor is HER2-receptor negative
4. The individual is axillary-node negative, with or without axillary-node micrometastasis 2.0 millimeters or less in size in one or more lymph nodes
5. The individual is a candidate for hormone therapy (e.g., tamoxifen or aromatase inhibitors) and adjuvant chemotherapy, and the results will guide whether or not to undergo adjuvant chemotherapy.

Breast Cancer Index, EndoPredict, MammaPrint, and Prosigna Gene Signature are investigative and unproven and therefore NOT COVERED for all other clinical presentations and conditions. There is insufficient reliable evidence in the form of high quality peer-reviewed medical literature to establish the efficacy or effects on health care outcomes.
All other gene expression profiles are investigative and unproven and therefore NOT COVERED, including but not limited to:

1. BluePrint®
2. BreastOncPx™ 14-Gene Assay
3. BreastPRS
4. Genomic Grade Index (aka MapQuant Dx™)
5. Mammostrat®
6. Oncotype Dx® Breast Cancer Assay for Ductal Carcinoma In Situ (DCIS)
7. Rotterdam Signature 76-Gene Assay
8. Symphony Genomic Profile
9. TargetPrint®
10. 41-Gene Prognostic Signature

There is insufficient reliable evidence in the form of high quality peer-reviewed medical literature to establish the efficacy or effects on health care outcomes.

The use of more than one gene expression profile assay per each breast cancer tumor type (either repeat testing of a previously performed assay or using a different assay) is investigative and unproven and therefore NOT COVERED. There is insufficient reliable evidence in the form of high quality peer-reviewed medical literature to establish the efficacy or effects on health care outcomes.

**Description**

A gene expression profile is a laboratory test that measures degree of expression of multiple genes from tumor tissue samples obtained during surgery for use in predicting (1) breast cancer recurrence and (2) potential treatment benefit from hormone therapy (i.e., tamoxifen or aromatase inhibitors) and/or adjuvant chemotherapy for patients diagnosed with early-stage breast cancer. Based on assay results, the individual’s breast cancer is classified into a risk category based on expression of the gene sets that were analyzed. Various genomic testing methodologies are used, including immunohistochemistry, fluorescence in situ hybridization (FISH), quantitative reverse transcription polymerase chain reaction (RT-qPCR), reverse transcription polymerase chain reaction (RT-PCR), and genomic microarray analysis.

Many gene expression profiles are purported for prediction of breast cancer recurrence. Examples include, but are not limited to:

1. **OncoType DX Breast Cancer Assay** is used for predicting the potential benefit of chemotherapy and likelihood of distant breast cancer recurrence within 10 years in women with Node (-) or Node (+), ER-positive, HER2-negative invasive breast cancer who will be treated with tamoxifen. It is also intended to assist in making decisions regarding adjuvant chemotherapy based on recurrence likelihood. Oncotype DX uses RT-qPCR to analyze the patterns of 21 genes correlated with relapse-free survival. Based on the levels of gene expression detected by the assay, patients are assigned a recurrence score from 0 to 100, in which a higher score indicates a greater risk of recurrence.

2. **Breast Cancer Index™ (BCI)** is a RT-PCR assay that tests two components: the BCI Prognostic risk of recurrence and the BCI Predictive likelihood of benefit. The Prognostic component of the BCI provides an individualized risk of late (5 to 10 years) distant recurrence and risk of overall (0 to 10 years) distant recurrence (if ordered at the time of diagnosis). The Predictive component provides prediction of benefit from extended (> 5 years) endocrine therapy for patients who are recurrence free after an initial 5 years of adjuvant endocrine therapy.

3. **EndoPredict®** (EP) is a RT-PCR assay of RNA from a tumor tissue sample that is used to calculate the EP score and the EPclin score to assess the risk of distant recurrence within 10 years of testing, as well as for the prediction of benefit from chemotherapy in patients with ER+, HER2(–) early-stage breast cancer when treated with 5 years of endocrine therapy.
4. **MammaPrint®** (aka Amsterdam 70-Gene Breast Cancer Recurrence Assay) is an index calculated using an algorithm that determines the molecular prognosis (high versus low risk of recurrence). A good prognosis signature occurs if the correlation coefficient of a tumor’s gene expression profile compared to the average profile of expression in those with a good-prognosis signature is greater than 0.4 (the threshold that resulted in a 10% false-negative rate). If those standards are not met, then a poor prognosis signature is determined. A good prognosis signature is further defined as the probability of > 90% for five-year distant metastasis–free survival.

5. **Prosigna™ Gene Signature** (aka PAM50 Breast Cancer Intrinsic Bioclassifier) provides a risk category and numerical score to assess a patient's risk of distant recurrence of disease at 10 years in postmenopausal women with Node (-) and stage I or II breast cancer or Node (+), HR(+), stage II breast cancer. Prosigna assay measures gene expression levels of RNA extracted from breast tumor tissue and generates a Risk of Recurrence (ROR) score to predict the probability of survival at 10 years for endocrine-treated HR(+) breast cancer.

**FDA Approval**

Genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. Premarket approval from the FDA is not required as long as the assay is performed in a laboratory facility that observes CLIA regulations and the test is not marketed for general distribution.

The Oncotype DX assay was developed by Genomic Health, Inc. and is currently performed only at Genomic Health Reference Laboratory (Redwood City, CA). Therefore, the Oncotype DX assay is not currently subject to FDA approval.

MammaPrint (Agendia, Inc.) was granted 510(k) FDA approval in February 2007 under the Premarket Notification process. Although not subject to FDA approval, Agendia sought approval as an FDA Class II in-vitro diagnostic multivariate index assay (IVDMIA). It was the first assay to be given IVDMIA FDA approval.

The Prosigna Breast Cancer Prognostic Gene Signature Assay (Laboratory Corporation of America) received FDA 510(k) clearance in September 2013.

Other gene expression profile assays not currently subject to FDA approval include, but are not limited to:

1. BluePrint (Agendia, Inc.)
2. Breast Cancer Index / Theros H/I Ratio (bioTheranostics)
3. BreastOncPx (US Labs)
4. BreastPRS (Signal Genetics)
5. EndoPredict (Svidon Diagnostics)
6. Genomic Grade Index (aka MapQuant Dx™) (Ipsogen, Inc.)
7. Mammostrat (Clariant, Inc.)
8. Oncotype Dx for Prognosis of Recurrence of Ductal Carcinoma In Situ (DCIS) Breast Cancer (Genomic Health, Inc.)
10. Rotterdam Signature 76-Gene Assay (Veridex LLC)
11. Symphony Genomic Profile (Agendia, Inc.)
12. TargetPrint (Agendia, Inc.)
13. 41-Gene Prognostic Signature

**Prior Authorization**

Prior authorization is not required. However, services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial may result if criteria are not met.
Coding Considerations
Use the current applicable CPT/HCPCS code(s). The following codes are included below for informational purposes only, and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

CPT Codes:
- 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
- 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

HCPC Code:
- S3854 – Gene expression profiling panel for use in the management of breast cancer treatment

Original Effective Date: 11/1/2007

Re-Review Date(s):
- 9/23/2008
- 9/27/2011
- 12/17/2014
- 1/1/2018 – administrative update; codes added
- 5/16/2018
- 2/12/2020 – administrative update; format
- 5/19/2021

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