Medical Policy

Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence with Risk Stratification (Including Oncotype DX™ and Other Tests)

Policy Number: OCA 3.572
Version Number: 18
Version Effective Date: 07/01/19

Product Applicability

- **All Plan+ Products**
  - Well Sense Health Plan
    - Well Sense Health Plan
  - Boston Medical Center HealthNet Plan
    - MassHealth
    - Qualified Health Plans/ConnectorCare/Employer Choice Direct
    - Senior Care Options ◊

Notes:
+ Disclaimer and audit information is located at the end of this document.
◊ The guidelines included in this Plan policy are applicable to members enrolled in Senior Care Options only if there are no criteria established for the specified service in a Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) on the date of the prior authorization request. Review the member’s product-specific benefit documents at [www.SeniorsGetMore.org](http://www.SeniorsGetMore.org) to determine coverage guidelines for Senior Care Options.

Policy Summary

The Plan considers Oncotype DX™ gene expression profiling of tumor tissue to be medically necessary for all members (regardless of gender) diagnosed with breast cancer when testing is used to predict the risk of breast cancer recurrence (prognostic component) and likelihood of benefit (predictive component) from extended endocrine therapy and/or adjuvant chemotherapy and all applicable medical criteria are met. **Plan prior authorization is required for all molecular and chromosomal genetic testing (including all gene expression profiling tests), except for prenatal genetic screening**

* Plan refers to Boston Medical Center Health Plan, Inc. and its affiliates and subsidiaries offering health coverage plans to enrolled members. The Plan operates in Massachusetts under the trade name Boston Medical Center HealthNet Plan and in other states under the trade name Well Sense Health Plan.
Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence with Risk Stratification, (Including Oncotype DX™ and Other Tests)

The Plan only covers gene expression profiling testing of tumor tissue for breast cancer recurrence with the Oncotype DX™; the use of Oncotype DX™ for any other indication, to predict recurrence with tumor tissue for any other type of cancer, or when Plan criteria are not met is considered investigational. Other types of gene expression profiling tests of tumor tissue used to predict breast cancer recurrence and/or the use of profiling tests of tumor tissue to predict other types of cancer recurrence or risk stratification are considered investigational. See the Plan’s Genetic/Genomic Testing and Pharmacogenetics medical policy, policy number OCA 3.727, rather than this policy for applicable medical criteria related to the following types of testing and indications: gene expression testing of tumor tissue to predict response to drug therapy and treatment; gene expression testing to diagnose indeterminate nodules or tumors as benign or malignant; testing of protein biomarkers using diagnostic blood tests, urine tests, or other testing methods such as immunofluorescence and automated quantitative images of biopsy tissue (rather than gene expression of tumor tissue) to predict cancer recurrence with risk stratification based on an established algorithm; and/or genetic testing to classify a tumor into a main cancer type and subtype to identify the primary tissue of origin in a member when there is clinical uncertainty of a tumor’s primary origin. Review the Plan’s Experimental and Investigational Treatment medical policy, policy number OCA 3.12, for the product-specific definitions of experimental and investigational treatment.

The Plan supports the National Comprehensive Cancer Network (NCCN) guidelines for genetic counseling for all genetic tests conducted with Plan members; NCCN recommends that adequate pre-test and post-test genetic counseling be provided by a health care professional with expertise in genetics. Genetic counseling provided to a Plan member or the member’s guardian if the member is under the age of 18 should be documented in the member’s medical record and conducted by an appropriately trained practitioner with expertise and experience in genetics, including a provider acting within the scope of the practitioner’s license and practice, clinical geneticist, or genetic counselor.

Plan prior authorization is required for all molecular and chromosomal genetic testing, except for prenatal genetic screening tests when the member is pregnant (as specified in the Applicable Coding section of this policy) and Plan criteria are met. See the following Plan policies for additional prior authorization guidelines for genetic testing available at www.bmchp.org for BMC HealthNet Plan

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members (or at www.SeniorsGetMore.org for Senior Care Options members) and www.wellsense.org for Well Sense Health Plan members:

1. Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies, policy number OCA 3.573

2. Genetic/Genomic Testing and Pharmacogenetics, policy number OCA 3.727∞

∞ Note: See the Plan’s Genetic/Genomic Testing and Pharmacogenetics medical policy, policy number OCA 3.727, rather than this policy for applicable medical criteria related to the following types of testing and indications: gene expression testing of tumor tissue to predict response to drug therapy and treatment; gene expression testing to diagnose indeterminate nodules, lesions, or tumors as benign or malignant; genomic testing of precancerous tumors to assess the risk of future cancer development (e.g., BBDRisk Dx™); testing of protein biomarkers using diagnostic blood tests, urine tests, or other testing methods such as immunofluorescence and automated quantitative images of biopsy tissue (rather than gene expression of tumor tissue) to predict cancer recurrence with risk stratification based on an established algorithm; and/or genetic testing to classify a tumor into a main cancer type and subtype to identify the primary tissue of origin in a member when there is clinical uncertainty of a tumor’s primary origin. Review the Plan’s Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence with Risk Stratification (Including Oncotype DX™ and Other Tests) medical policy, policy number OCA 3.572, for medical criteria for gene expression profiling of tumor tissue to predict cancer recurrence with risk stratification.

3. Genetic Testing for Familial Malignant Melanoma, policy number OCA 3.78

4. Genetic Testing for Fragile X-Associated Disorders, policy number OCA 3.571

5. Genetic Testing for Hereditary Breast and Ovarian Cancer Syndrome, policy number OCA 3.57

6. Genetic Testing for Hereditary Colorectal Cancer, policy number OCA 3.64

7. Genetic Testing for Hereditary Thrombophilia, policy number OCA 3.728

8. Preimplantation Genetic Testing, policy number OCA 3.726

Description of Item or Service

Gene Expression Profiling/Genomic Assay: A laboratory test that measures the expression of a group of genes and translates the gene expression information into a risk score for a given disease or condition (e.g., recurrence of primary breast cancer). Genetic tests can estimate an individuals’ risk of developing a disease in the future. Gene expression tests measure the activity of RNA in a tissue or

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bodily fluid at a given point in time to provide information on the individual’s current disease state, predict an individual’s response to treatment, or predict the likelihood of future disease with risk stratification; RNA levels change over time based on pathological conditions and environmental signals.

**Oncotype DX™ Breast Cancer Assay/21-Gene Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) Assay:** A multiple gene expression assay of 21 genes performed on tumor tissue from individuals with newly diagnosed, early-stage (stage 1 or II), estrogen receptor positive (ER+), node negative (N-) breast cancer to predict the risk of recurrence. The assay is used to guide use of adjuvant endocrine therapy (e.g., tamoxifen, aromatase inhibitors) and adjuvant chemotherapy. Formalin-fixed paraffin-embedded (FFPE) tumor samples are analyzed, measuring the messenger (mRNA) expression levels of 16 genes which are markers for proliferation and recurrence; test results are used to quantify the probability of breast cancer recurrence. Oncotype DX™ Breast Cancer Assay is developed by Genomic Health Inc. and is intended as a prognostic test and as a predictive test for response to chemotherapy for individuals with targeted types of breast cancer.

**Medical Policy Statement**

The Plan considers Oncotype DX™ (Genomic Health) gene expression profiling of tumor tissue to be medically necessary for all members (regardless of gender) diagnosed with breast cancer when testing is used to predict the risk of breast cancer recurrence (prognostic component) and likelihood of benefit (predictive component) from extended endocrine therapy and/or adjuvant chemotherapy when ALL of the following criteria are met and documented in the medical record, as specified below in items 1 through 7:

1. Oncotype DX™ is ordered by the physician supervising the adjuvant therapy; AND

2. Tumor is unilateral and non-fixed; AND

3. Disease is stage I or II; AND

4. There is no evidence of distant metastatic breast cancer; AND

5. The member is a candidate for adjuvant chemotherapy and testing is being done specifically to guide the decision as to whether or not adjuvant chemotherapy will be used; AND

6. Oncotype DX™ is ordered within six (6) months after diagnosis of breast cancer and/or surgical treatment (since the value of delayed chemotherapy is unknown); AND
7. The tumor has ALL of the following characteristics based on post-operative pathological evaluation, as specified below in items a through h:

a. Tumor is ONE (1) of the following types, as specified below in items (1) through (4):

   (1) Infiltrating ductal; OR
   (2) Infiltrating lobular; OR
   (3) Metaplastic; OR
   (4) Mixed; AND

b. Histology of tumor is not tubular or colloid; AND

c. Lymph node status meets ONE (1) of the following criteria, as specified below in items (1) through (3):

   (1) Axillary-node negative; OR
   (2) Axillary-node micrometastases (200 cells, > 0.2 mm but none > 2.0 mm); OR
   (3) 1 to 3 involved ipsilateral axillary lymph nodes and/or internal mammary nodes (or micrometastases or macrometastases by sentinel lymph node biopsy) to guide the addition or combination chemotherapy to standard hormone therapy; AND

d. Tumor size is greater than 0.5 cm in diameter; AND

e. Tumor is unifocal; AND

f. Hormone receptor positive (i.e., estrogen receptor positive [ER+] AND/OR progesterone receptor positive [PR+]); AND

g. Human epidermal growth factor receptor 2 (HER2/neu) negative; AND

h. Tumor is not a pT4 lesion.
Limitations

1. Repeat Oncotype DX™ testing and/or testing of multiple tumor sites in the same person are NOT considered medically necessary.

2. Oncotype DX™ testing for indications other than those listed in the Medical Policy Statement section is NOT considered medically necessary and requires Plan Medical Director review and approval (including but not limited to the Oncotype DX™ Colon Cancer Assay and Oncotype DX™ Genomic Prostate Score Cancer Assay by Genomic Health Inc.).

3. Oncotype DX™ testing for the prognosis of recurrence of ductal carcinoma in situ (DCIS) breast cancer is NOT considered medically necessary (e.g., Oncotype DX Breast Cancer DCIS Score by Genomic Health Inc.).

4. The Oncotype DX™ is the only test the Plan considers medically necessary for gene expression profiling of breast cancer tissue when applicable Plan criteria are met; other gene expression profiling tests of breast cancer tissue are considered either investigational or not medically necessary as an alternative to Oncotype DX, including but not limited to BluePrint™/BluePrint Molecular Subtyping Signature (also known as the 80-gene profile by Agendia Inc.), Breast Cancer Index BCI (bio Thranostics Inc.), EndoPredict (Myriad Genetics), Ki-67 (MKI67) proliferation marker testing (ARUP Laboratories, Baylor College of Medicine, Laboratory Corporation of America, and Quest Diagnostics Inc.), MammaPrint 70-Gene Breast Cancer Recurrence Assay (also known as Amsterdam Signature or 70-gene profile by Agendia Inc.), and/or the Prosigna™ Breast Cancer Prognostic Gene Signature Assay (NanoString Technologies Inc.).

5. Other types of gene expression profiling tests of tumor tissue used to predict recurrence of any type of cancer and/or determine risk stratification (including gene expression analysis using a proprietary risk classifier to categorize indeterminate lesions or tumors, as determined from biopsy specimen) are considered investigational unless specified as medically necessary in the Medical Policy Statement section of this policy and applicable criteria are met. Examples of investigational tests include but are not limited to the following: DecisionDx-GBM™ (Castle Biosciences Inc.) for glioblastoma multiforme, Decipher® Prostatic Cancer Classifier (GenomeDx Biosciences Corp.), DecisionDx™-Melanoma (Castle Biosciences Inc.) for melanoma, DecisionDx®-UM (Castle Biosciences Inc.) for uveal melanoma, MyPRS™ Plus (Signal Genetics LLC) for myeloma, and Prolaris® (Myriad Genetics) for prostate cancer.

See the Plan’s Genetic/Genomic Testing and Pharmacogenetics medical policy, policy number OCA 3.727, rather than this policy for applicable medical criteria related to the following types and indications for testing: gene expression testing to predict response to drug therapy and treatment; gene expression testing to diagnose indeterminate nodules or tumors as benign or malignant (e.g., Afirma Thyroid FNA Analysis by Veracyte Inc.); genomic testing of precancerous tumors to assess the
risk of future cancer development (e.g., BBDRisk Dx™); testing of protein biomarkers using diagnostic blood tests, urine tests, or other testing methods such as immunofluorescence and automated quantitative images of biopsy tissue (rather than gene expression of tumor tissue) to predict cancer recurrence with risk stratification based on an established algorithm; and/or genetic testing to classify a tumor into a main cancer type and subtype to identify the primary tissue of origin in a member when there is clinical uncertainty of a tumor’s primary origin. Review additional, applicable Plan medical policies related to genetic testing, as specified at the end of this policy and posted at www.bmchp.org for BMC HealthNet Plan members and at www.wellsense.org for Well Sense Health Plan members.

Definitions

**Breast Cancer Index (BCI):** A real-time reverse transcription PCR (RT-PCR) assay (by bio Theranostics Inc.) performed using formalin-fixed paraffin-embedded tissue. The test has two (2) components: the BCI Prognostic (risk of recurrence) and BCI Predictive (likelihood of benefit). The prognostic component combines two (2) indexes to provide an individualized risk of late (i.e., 5 to 10 years post-diagnosis) distant recurrence and risk of overall (0 to 10 years post-diagnosis) distant recurrence for breast cancer. The Plan considers this test experimental and investigational due to insufficient data supporting the analytical validity, clinical validity, and clinical utility of the test. See the Limitations section of this policy for applicable Plan guidelines.

**Decipher Prostate Cancer Classifier:** A multigene test (by GenomeDx Biosciences Corp.) of 22 RNA biomarkers associated with aggressive prostate cancer to predict the likelihood of metastasis following prostatectomy in high-risk individuals. The Plan considers this test experimental and investigational due to insufficient data supporting the analytical validity, clinical validity, and clinical utility of the test. See the Limitations section of this policy for applicable Plan guidelines.

**DecisionDx-GBM Test:** A multigene expression assay (by Castle Biosciences Inc.) designed to predict which patients diagnosed with glioblastoma multiforme are likely to experience long-term (i.e., greater than two [2] years) progression-free survival. The Plan considers this test experimental and investigational due to insufficient data supporting the analytical validity, clinical validity, and clinical utility of the test. See the Limitations section of this policy for applicable Plan guidelines.

**DecisionDx™-Melanoma Test:** A multigene expression assay (by Castle Biosciences Inc.) designed to predict distant metastasis in stage 1 and stage 2 melanoma patients. DecisionDx™-Melanoma assesses the expression of 31 genes that have been associated with metastasis and classifies tumors as Class 1 (low risk of metastasis) or Class 2 (high risk of metastasis). The test is performed using reverse transcription polymerase chain reaction (RT-PCR) on formalin-fixed paraffin-embedded (FFPE) melanoma specimens. The Plan considers this test experimental and investigational due to insufficient data supporting the analytical validity, clinical validity, and clinical utility of the test. See the Limitations section of this policy for applicable Plan guidelines.
**DecisionDx®-UM Test:** A multigene expression profiling test (by Castle Biosciences Inc.) intended for use in patients with uveal melanoma. The test measures gene expression using reverse transcription PCR (RT-PCR) of a set of 15 genes (including three [3] controls) within an ocular melanoma tumor to identify the likelihood of metastasis within 5 years. The DecisionDx®-UM stratifies tumors into three (3) risk classes to aid with prognosis. The Plan considers this test experimental and investigational due to insufficient data supporting the analytical validity, clinical validity, and clinical utility of the test. See the Limitations section of this policy for applicable Plan guidelines.

**EndoPredict:** Reverse transcription PCR (RT-PCR) assay (by Myriad Genetics) of RNA isolated from tumor tissue samples from a formalin-fixed paraffin-embedded block or a core needle biopsy that is used to assess the risk of distant breast cancer recurrence within 10 years of testing and to predict the benefit of chemotherapy. The Plan considers this test experimental and investigational due to insufficient data supporting the clinical utility of the test. See the Limitations section of this policy for applicable Plan guidelines.

**Fluorescence In Situ Hybridization (FISH):** A test that maps specific genes or portions of genes. FISH testing is done on breast cancer tissue removed during biopsy to see if the cells have extra copies of the HER2 gene. The more copies of the HER2 gene that are present, the more HER2 receptors the cells have. These HER2 receptors receive signals that stimulate the growth of breast cancer cells. The FISH test results will determine if the cancer is either “positive” or “negative” (a result sometimes reported as “zero”) for HER2. Generally, the FISH test is not as widely available as another method of HER2 testing, called immunohistochemistry, or IHC. However, FISH is considered more accurate. In many cases, a lab will do the IHC test first, ordering FISH only if the IHC results don’t clearly show whether the cells are HER2-positive or negative.

**Formalin Fixed Paraffin-Embedded (FFPE) Tumor Tissue:** Tissue samples derived from tissues (usually suspected tumor samples) that are fixed with formalin to preserve the cytoskeletal and protein structure and then embedded in a type of paraffin wax so the tissue can be sliced on a microtome, an instrument used to prepare very fine slices. Formalin irreversibly cross-links proteins via the amino groups thus preserving the structural integrity of the cells so they can be stained with dyes used to analyze for abnormalities in the tissue that indicate cancer.
Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence with Risk Stratification, (Including Oncotype DX™ and Other Tests)

Genetic Testing: According to U.S. Library of Medicine, genetic testing is defined as a type of medical test that identifies changes in chromosomes, genes, or proteins. The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person’s chance of developing or passing on a genetic disorder. More than 1,000 genetic tests are currently in use, and more are being developed. Several methods can be used for genetic testing:

1. Molecular genetic tests (or gene tests) study single genes or short lengths of DNA to identify variations or mutations that lead to a genetic disorder.

2. Chromosomal genetic tests analyze whole chromosomes to see if there are large genetic changes, such as an extra copy of a chromosome or missing DNA, that cause a genetic condition.

3. Biochemical genetic tests study the amount or activity level of proteins; abnormalities in either can indicate changes to the DNA that result in a genetic disorder.

Immunohistochemistry (IHC): A special staining process performed on fresh or frozen breast cancer tissue removed during biopsy. IHC is used to show whether or not the cancer cells have HER2 receptors and/or hormone receptors on their surface. This information plays a critical role in treatment planning. The IHC test gives a score of 0 to 3+ that measures the amount of HER2 receptor protein on the surface of cells in a breast cancer tissue sample. If the score is 0 to 1+, it’s called “HER2 negative.” If the score is 2+, it's called "borderline." A score of 3+ is called “HER2 positive.”

MammaPrint 70-Gene Breast Cancer Recurrence Assay: Gene expression profile (by Agendia) using fresh frozen or formalin fixed paraffin-embedded tissue to calculate the risk of breast cancer recurrence and the need for systemic therapy with an algorithm used to determine the molecular prognosis (high versus low risk of recurrence). The Food and Drug Administration (FDA) cleared MammaPrint as a test to evaluate the risk for distant metastasis following resection in stage I, lymph node–negative breast cancer patients when combined with clinicopathologic models. See the Limitations section of this policy for applicable Plan guidelines.

Multigene Panel Tests: Tests that evaluate more than one (1) gene simultaneously to detect changes in these genes’ sequence and expression most commonly associated with certain diseases and other genes that may have limited evidence of an association to the disorder. Multigene panel tests may involve traditional exon-by-exon sequencing of targeted genes to identify genetic variants or use next-generation sequencing. Each laboratory establishes its own set of criteria for selecting the genes represented in a panel, even when panels are used for the same or similar clinical indications. The lack of regulatory oversight of genetic testing means that laboratories can change the components of a panel at any time, making it difficult to evaluate the clinical utility of multigene panel tests. See the Genetic/Genomic Testing and Pharmacogenetics medical policy, policy number OCA 3.727, rather than this policy for Plan guidelines related to multigene panel testing.

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**Oncotype DX Colon Cancer Assay:** A reverse transcription PCR (RT-PCR)-based profiling test (by Genomic Health Inc.) that measures the RNA gene expression pattern of 12 genes (7 associated with recurrence and 5 reference genes) from formalin-fixed paraffin-embedded tumor tissue from a patient with stage II or stage III colon cancer. A proprietary algorithm is used to calculate a recurrence score that quantifies patient risk for colon cancer recurrence. The Plan considers this test experimental and investigational due to insufficient data supporting the analytical validity, clinical validity, and clinical utility of the test. See the Limitations section of this policy for applicable Plan guidelines.

**Oncotype DX Genomic Prostate Score (GPS) Assay:** A reverse transcription PCR (RT-PCR)-based profiling test that measures the RNA gene expression pattern of 17 genes (12 genes linked to biological pathways in prostate cancer and five (5) reference genes from fixed paraffin-embedded prostate tumor tissue. A genomic prostate score is calculated to predict tumor aggressiveness. The Plan considers this test experimental and investigational due to insufficient data supporting the analytical validity, clinical validity, and clinical utility of the test. See the Limitations section of this policy for applicable Plan guidelines.

**Prolaris Prostate Cancer Prognostic Test:** An in vitro prognostic assay that measures gene expression in tumor samples isolated from prostate cancer patients. The Prolaris test (by Myriad Genetics) provides a personalized score indicative of the patient’s tumor aggressiveness and provides a 10-year, prostate cancer–specific mortality risk score. The Plan considers this test experimental and investigational due to insufficient data supporting the clinical utility of the test. See the Limitations section of this policy for applicable Plan guidelines.

**Prosigna Breast Cancer Prognostic Gene Signature Assay:** A gene expression test (by NanoString Technologies Inc.) used as a prognostic indicator for distant recurrence-free survival at 10 years in postmenopausal women with hormone receptor positive (HR+) breast cancer that are either lymph node negative and stage I or II breast cancer, or lymph node–positive (one [1] to three [3] positive nodes) stage II breast cancer and to be treated with adjuvant endocrine therapy alone, when used in conjunction with other clinicopathologic factors.

**pT4 Pathologic Staging of Breast Tumor:** Breast tumor of any size with direct extension to chest wall or skin. Clinical information may be required to designate a tumor as pT4. Dermal invasion alone (without ulceration, satellite nodules, or inflammatory breast cancer) does not alter T category; such cases are classified as T1, T2, or T3, depending on tumor size. pT4 is categorized as:

1. **pT4a:** Extension to chest wall, not including pectoralis muscle

2. **pT4b:** Edema (including peau d’orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast

3. **pT4c:** Both T4a and T4b

4. **pT4d:** Inflammatory carcinoma

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Reverse Transcriptase-Polymerase Chain Reaction/Reverse Transcription PCR (RT-PCR): Technique to detect and quantify messenger RNA (mRNA). The technique consists of two (2) parts: the synthesis of complementary DNA (cDNA) from RNA by reverse transcription (RT); and the amplification of a specific cDNA of the polymerase chain reaction (PCR).

Tumor, Node, Metastasis (TNM) Staging System for Breast Cancer: Internationally accepted system by the American Joint Committee on Cancer (AJCC) used to determine the stages of breast cancer to estimate prognosis and guide clinical management. The TNM staging system correlates important tumor characteristics with survival data to help estimate and follow outcomes. The eighth edition of the TNM staging system is effective as of January 1, 2018 and relies on tumor size, involvement of lymph nodes, presence of metastatic disease, and biologic markers.

1. Stage I: Early stage breast cancer with either no evidence of the primary tumor or a primary tumor size ≤ 20 mm in its greatest dimension. Stage 1 breast cancer may include either no regional lymph node metastasis or micrometastases (200 cells, > 0.2 mm but none > 2.0 mm) with no clinical or radiographic evidence of distant metastasis. Stage I classification of breast cancer is further categorized as IA or IB based on the clinical and pathological presentation of primary tumor and node involvement.

2. Stage II: Early stage breast cancer with either no evidence of the primary tumor or a primary tumor of varying sizes (as large as > 50 mm in its greatest dimension). Stage II breast cancer may include either no regional lymph node metastasis, micrometastases, metastases in 1-3 axillary lymph nodes and/or in internal mammary nodes, and/or in clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy. There is no clinical or radiographic evidence of distant metastasis. Stage II classification of breast cancer is further categorized as IIA or IIB based on the clinical and pathological presentation of primary tumor and node involvement.

3. Stage III: More advanced breast cancer in which there is varying degree of tumor presentation, from no evidence of primary tumor up to a tumor of any size (with or without direct extension to the chest wall and/or to the skin). There is no clinical or radiographic evidence of distant metastasis. Stage III classification of breast cancer is further categorized as IIIA, IIIB, and IIIC based on the severity of the clinical and pathological presentation of tumor, node involvement, and extension to surrounding areas. (Note: Recurrent breast cancer or bilateral breast cancer is categorized as stage III or stage IV according to the National Comprehensive Cancer Network.)

4. Stage IV: Metastatic breast cancer detected by clinical and radiological means that has spread outside the breast to other organs in the body, such as the bones, lungs, liver, or brain. Stage IV is an advanced breast cancer in which there is varying degree of tumor presentation, from no evidence of primary tumor up to a tumor of any size and may include any type of node...
Whole Exome Sequencing (WES)/Whole Genome Sequencing (WGS): Sequencing the protein coding regions (called exons) of all of an individual’s genes (known as the exome). While exons represent only 1% of the genome, they account for approximately 85% of disease-causing variants. Through identification of variants across the exome, WES avoids the need to run multiple single-gene tests, which require prior information about variants affecting the disease. WES has been performed in a number of cancers, whereby comparison between tumor DNA and normal DNA from the same individual allows identification of variants specific to the tumor, which may provide information used for diagnosis and treatment. WES is targeted sequencing of the subset of the human genome that contains functionally important sequences of protein-coding DNA, while whole genome sequencing (WGS) uses next-generation sequencing techniques to sequence both coding and non-coding regions of the genome. See the Plan’s Genetic/Genomic Testing and Pharmacogenetics medical policy, policy number OCA 3.727, rather than this policy for Plan guidelines related to WES and WGS.

Applicable Coding

The Plan uses and adopts up-to-date Current Procedural Terminology (CPT) codes from the American Medical Association (AMA), International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) diagnosis codes developed by the World Health Organization and adapted in the United Stated by the National Center for Health Statistics (NCHS) of the Centers for Disease Control under the U.S. Department of Health and Human Services, and the Health Care Common Procedure Coding System (HCPCS) established and maintained by the Centers for Medicare & Medicaid Services (CMS). Since the AMA, NCHS, and CMS may update codes more frequently or at different intervals than Plan policy updates, the list of applicable codes included in this Plan policy is for informational purposes only, may not be all inclusive, and is subject to change without prior notification. Whether a code is listed in the Applicable Coding section of this Plan policy does not constitute or imply member coverage or provider reimbursement. Providers are responsible for reporting all services using the most up-to-date industry-standard procedure and diagnosis codes as published by the AMA, NCHS, and CMS at the time of the service.

Providers are responsible for obtaining prior authorization for the services specified in the Medical Policy Statement section and Limitation section of this Plan policy, even if an applicable code appropriately describing the service that is the subject of this Plan policy is not included in the Applicable Coding section of this Plan policy. Coverage for services is subject to benefit eligibility under the member’s benefit plan. Please refer to the member’s benefits document in effect at the time of the service to determine coverage or non-coverage as it applies to an individual member. See Plan reimbursement policies for Plan billing guidelines. Review the Plan’s Genetic/Genomic Testing and Pharmacogenetics medical policy, policy number OCA 3.727, for additional guidelines regarding genetic testing. Plan prior authorization is required for all molecular and chromosomal genetic testing unless otherwise specified in an applicable Plan medical policy.
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**CPT Code** | **Description: Code Covered When Medically Necessary**
---|---
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

Plan note: Use this code when billing for the Oncotype DX™ Breast Cancer Assay.

**HCPCS Code** | **Description: Code Covered When Medically Necessary**
---|---
None

**CPT Codes** | **Description: Codes Considered Experimental and Investigational**
---|---
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

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

81541 | Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score

81525 | Oncology (colon), 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 a recurrence score

0081U | Oncology (uveal melanoma), mRNA, gene-expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping genes), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis

Plan note: PLA code is only billable when the DecisionDx®-UM (Castle Biosciences, Inc.) test is performed. Code is ONLY payable for the Senior Care Options (SCO) products.

0089U | Oncology (melanoma), gene expression profiling by RTqPCR, <i>PRAME</i> and <i>LINC00518</i>, superficial collection using adhesive patch(es)

Plan Note: PLA code is only billable when the Pigmented Lesion Assay (DermTech) is performed. Code is ONLY payable for the SCO products.
Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a categorical result (ie, benign, indeterminate, malignant)

PLA code is only billable when the myPath Melanoma (Myriad Genetic Laboratories) test is performed. Code is ONLY payable for the SCO products.

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description: Code Considered Experimental and Investigational</th>
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<tbody>
<tr>
<td>S3854</td>
<td>Gene expression profiling panel for use in the management of breast cancer treatment</td>
</tr>
<tr>
<td></td>
<td>Plan note: Use this code when billing for all gene expression profiling tests of breast cancer tissue except the Oncotype DX™ Breast Cancer Assay.</td>
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Clinical Background Information

Oncotype DX™ Breast Cancer Assay is used to quantify the likelihood of distant recurrence in an individual with breast cancer, and can be helpful 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. RNA is extracted from the tumor tissue, 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. The score is calculated from the gene expression results using a proprietary Oncotype DX™ algorithm and 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 score correlates with a specific likelihood of distant recurrence at 10 years.

The MammaPrint® (Agendia Inc.) assay uses a microarray technology platform to analyze the expression of 70 genes from tumor samples that are fresh frozen or placed in an RNA molecular fixative solution provided in a kit from the manufacturer. Agendia now accepts formalin-fixed paraffin-embedded (FFPE) specimens for analysis as well as fresh frozen samples. In the United States, the MammaPrint® assay is intended for patients with breast cancer who are stage I or II, are lymph node negative, and have a tumor size < 5.0 centimeters (cm). Additional indications for MammaPrint® used outside of the United States include patients who are either estrogen receptor positive (ER+) or negative (ER-) and patients who are either lymph node positive or negative. Currently, the Plan considers this test to not be medically necessary as an alternative to Oncotype DX™ (the 21-gene assay). According to the National Comprehensive Cancer Network (NCCN) Version 1.2016 Breast Cancer Guidelines, “the NCCN Panel members acknowledge that many assays, including PAM50 and MammaPrint, have been clinically validated for prediction of prognosis. However, based on the current available data, the panel believes that the 21-gene assay has been best-validated for its use as a prognostic test as well as in predicting who is most likely to respond to systemic chemotherapy.”
The BluePrint® molecular subtyping profile is an 80-gene expression profile that is designed to characterize breast tumors as basal-type, luminal-type, and ERBB2 (commonly referred to as HER2/neu)-type breast cancers. The manufacture (Agendia Inc.) claims that BluePrint® complements the MammaPrint® to allow for a more refined prediction of distant recurrence in patients at increased risk of recurrence by MammaPrint® and validates the prediction of low risk or recurrence by MammaPrint®. The Plan considers this test experimental and investigational.

Prosigna™ Breast Cancer Prognostic Gene Signature Assay (NanoString Technologies Inc.) is used with female breast cancer patients (as defined by the manufacturer) who have undergone surgery in conjunction with locoregional treatment consistent with standard of care. The test is a prognostic indicator for distant recurrence–free survival at 10 years in postmenopausal women (as defined by the manufacturer) with hormone receptor positive (HR+), lymph node negative or lymph node positive (up to 1-3 positive nodes), stage I or II breast cancer to be treated with adjuvant endocrine therapy alone, when used in conjunction with other clinicopathological factors. The Plan considers the test investigational at this time. Prosinga is performed using messenger RNA (mRNA) isolated from formalin-fixed paraffin-embedded (FFPE) breast tumor specimens or tissue slides. The set of 46 genes included in the assay is based upon PAM50, a 50-gene expression classifier that distinguishes between intrinsic breast cancer tissue subtypes that are associated with different rates of recurrence.

The Food and Drug Administration (FDA) only regulates genetic tests sold as kits and has practiced enforcement discretion for laboratory-developed tests (LDTs), which represent the majority of genetic tests marketed in the United States. While the Centers of Medicare & Medicaid Services (CMS) does not regulate the clinical laboratories in which LDTs are performed, CMS does not evaluate whether the genetic tests are clinically meaningful.

At the time of the Plan’s most recent policy review, the Centers for Medicare & Medicaid Services (CMS) has implemented the following national coverage determinations (NCDs) related to genetic tests: NCD for Colorectal Cancer Screening Tests (210.3) for coverage of immunoassay and guaiac fecal occult blood tests and the Cologuard™ - Multitarget Stool DNA (sDNA) test when CMS applicable criteria are met, NCD for Pharmacogenomic Testing for Warfarin Response (90.1) for medically necessary indications for testing as determined by CMS, and NCD for Cytogenetic Studies (190.3) for coverage based on CMS guidelines. CMS has determined that next generation sequencing (NGS) is reasonable and necessary as a diagnostic laboratory test and is covered nationally when performed in a CLIA-certified laboratory, when ordered by a treating physician, and when applicable CMS requirements are met, as specified in the CMS national coverage analysis (NCA) CAG-00450N. Medicare uses a combination of national and local coverage determinations for making coverage decisions for genetic tests. Medicare administrative contractors (MAC) may implement local coverage determinations (LCDs) that apply only within their own jurisdictions. Verify if applicable CMS criteria are in effect (through an NCD, LCD, or other CMS guidelines) for the specified genetic test, product name, site-specific gene analysis, and the indication for testing on the date of the prior authorization request for a Senior Care Options member.
References


Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence with Risk Stratification, (Including Oncotype DX™ and Other Tests)


Hayes Genetic Test Evaluation Overview. Decipher Prostate Cancer Classifier (GenomeDx BioSciences Corp.). Winifred Hayes, Inc. 2015 Sep 10.


Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence with Risk Stratification, (Including Oncotype DX™ and Other Tests)

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### Policy History

<table>
<thead>
<tr>
<th>Original Approval Date</th>
<th>Original Effective Date and Version Number</th>
<th>Policy Owner</th>
<th>Original Policy Approved by</th>
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</thead>
<tbody>
<tr>
<td>Regulatory Approval:  N/A</td>
<td>02/01/12 Version 1</td>
<td>Medical Policy Manager as Chair of MPCTAC</td>
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<tr>
<td>Internal Approval: 10/19/11: Medical Policy, Criteria, and Technology Assessment Committee (MPCTAC) 11/29/11: Quality Improvement Committee (QIC)</td>
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*Effective Date for the BMC HealthNet Plan Commercial Product(s): 01/01/12
*Effective Date for the Well Sense Health Plan New Hampshire Medicaid Product(s): 01/01/13
*Effective Date for the Senior Care Options Product(s): 01/01/16

### Policy Revisions History

<table>
<thead>
<tr>
<th>Review Date</th>
<th>Summary of Revisions</th>
<th>Revision Effective Date and Version Number</th>
<th>Approved by</th>
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<tr>
<td>07/01/12</td>
<td>Off cycle review of Well Sense Health Plan, revised Summary section, reformatted Medical Policy Statement section, deleted diagnosis codes, and revised language in Applicable Coding section.</td>
<td>Version 2</td>
<td>08/03/12: MPCAC 09/05/12: QIC</td>
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<tr>
<td>09/01/12</td>
<td>Review for effective date 01/01/13. Revised policy title, specified in Summary section that Plan prior authorization is required and referenced the Plan’s <em>Medically Necessary</em> policy and the <em>Experimental and Investigational Treatment</em> policy, updated language in Applicable Coding section, removed diagnosis codes because diagnosis codes do not change prior authorization requirement, updated and added references. Added limitation on testing of multiple tumor sites in the same person.</td>
<td>01/01/13 Version 3</td>
<td>09/19/12: MPCTAC 10/24/12: QIC</td>
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<tr>
<td>08/14/13 and 08/15/13</td>
<td>Off cycle review for Well Sense Health Plan and merged policy format. Incorporate policy revisions dated</td>
<td>Version 4</td>
<td>08/14/13: MPCTAC (electronic vote) 08/15/13: QIC</td>
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Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence with Risk Stratification, (Including Oncotype DX™ and Other Tests)

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<tr>
<td>09/01/12</td>
<td>(as specified above) for the Well Sense Health Plan product; these policy revisions were approved by MPCTAC on 09/19/12 and QIC on 10/24/12 for applicable Plan products.</td>
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<td>10/01/13</td>
<td>Review for effective date 02/01/14. Revised title, Summary section, and Limitations section. Revised criteria in the Medical Policy Statement section. Updated Definitions section and references. Added Plan note to the Applicable Coding section.</td>
<td>02/01/14 Version 5</td>
<td>10/16/13: MPCTAC 11/21/13: QIC</td>
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<td>07/01/14</td>
<td>Review for effective date 08/01/14. Updated Summary section. Added reference.</td>
<td>08/01/14 Version 6</td>
<td>07/21/14: MPCTAC (electronic vote) 07/24/14: QIC (electronic vote)</td>
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<td>10/01/14, 11/01/14, and 12/01/14</td>
<td>Review for effective date 03/01/15. Revised Summary, Description of Item or Service, Clinical Background Information, and References sections. Updated criteria in the Medical Policy Statement and Limitations sections. Revised title to include “Risk Stratification.” Added CPT code 81519 as an applicable code.</td>
<td>03/01/15 Version 7</td>
<td>10/15/14: MPCTAC 11/12/14: QIC 12/02/14: MPCTAC (electronic vote) 12/10/14: QIC</td>
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<td>11/25/15</td>
<td>Review for effective date 01/01/16. Updated template with list of applicable products and notes. Revised language in the Applicable Coding section.</td>
<td>01/01/16 Version 8</td>
<td>11/18/15: MPCTAC 11/25/15: MPCTAC (electronic vote) 12/09/15: QIC</td>
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<td>01/01/16</td>
<td>Annual review for effective date 05/01/16. Revised criteria in the Medical Policy Statement and Limitations sections. Updated Summary, Description of Item or Service, Clinical Background Information, and References sections. Revised the applicable code list.</td>
<td>05/01/16 Version 9</td>
<td>01/20/16: MPCTAC 02/10/16: QIC</td>
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<td>07/01/16</td>
<td>Industry-wide addition of applicable HCPCS code S3854 effective 07/01/16.</td>
<td>07/01/16 Version 10</td>
<td>Not applicable because industry-wide code addition.</td>
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<td>09/28/16</td>
<td>Review for effective date 11/01/16. Administrative changes made to clarify language related to gender.</td>
<td>11/01/16 Version 11</td>
<td>09/30/16: MPCTAC (electronic vote) 10/12/16: QIC</td>
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<th>Reviewers</th>
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<td>12/01/16</td>
<td>Review for effective date 02/01/17. Revised the Summary, Definitions, Clinical Background Information, References, and References to Applicable Laws and Regulations sections. Clarified language in the Limitations section without changing criteria.</td>
<td>02/01/17</td>
<td>12/21/16: MPCTAC</td>
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<td>06/01/17</td>
<td>Review for effective date 07/01/17. Administrative change made to the Limitations section to be consistent with the Summary section.</td>
<td>06/01/17</td>
<td>06/21/17: MPCTAC</td>
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<td>12/01/17</td>
<td>Review for effective date 01/01/18. Industry-wide updates to codes included in the Applicable Coding section.</td>
<td>01/01/18</td>
<td>Not applicable because industry-wide code changes.</td>
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<td>12/20/17</td>
<td>Review for effective date 03/09/18. Revised criteria in the Medical Policy Statement and Limitations sections. Administrative changes made to the Policy Summary, Definitions, and References sections. Revised policy title.</td>
<td>03/09/18</td>
<td>12/20/17: MPCTAC</td>
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<td>09/01/18</td>
<td>Review for effective date 10/01/18. Administrative changes made to the Policy Summary, Medical Policy Statement, Limitations, and Other Applicable Policies sections.</td>
<td>10/01/18</td>
<td>09/19/18: MPCTAC</td>
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<td>12/01/18</td>
<td>Review for effective date 03/01/19. Administrative changes made to the Policy Summary, Description or Item or Service, Limitations, Definitions, Clinical Background Information, References, Other Applicable Policies, and Reference to Applicable Laws and Regulations. Industry-wide code update in the Applicable Coding section. Revised criteria in the Medical Policy Statement section.</td>
<td>03/01/19</td>
<td>12/19/18: MPCTAC</td>
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<td>06/01/19</td>
<td>Review for effective date 07/01/19. Industry-wide code additions and Plan note added to the Applicable Coding section.</td>
<td>07/01/19</td>
<td>Not applicable because industry-wide code updates.</td>
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Reference to Applicable Laws and Regulations


MGL c 111 § 70G. Massachusetts General Law. Clinical Laboratories. Genetic information and reports protected as private information; prior written consent for genetic testing.


Disclaimer Information: +

Medical Policies are the Plan’s guidelines for determining the medical necessity of certain services or supplies for purposes of determining coverage. These Policies may also describe when a service or supply is considered experimental or investigational, or cosmetic. In making coverage decisions, the Plan uses these guidelines and other Plan Policies, as well as the Member’s benefit document, and when appropriate, coordinates with the Member’s health care Providers to consider the individual Member’s health care needs.

Plan Policies are developed in accordance with applicable state and federal laws and regulations, and accrediting organization standards (including NCQA). Medical Policies are also developed, as appropriate, with consideration of the medical necessity definitions in various Plan products, review of current literature, consultation with practicing Providers in the Plan’s service area who are medical experts in the particular field, and adherence to FDA and other government agency policies. Applicable state or federal mandates, as well as the Member’s benefit document, take precedence over these guidelines. Policies are reviewed and updated on an annual basis, or more frequently as needed. Treating providers are solely responsible for the medical advice and treatment of Members.

The use of this Policy is neither a guarantee of payment nor a final prediction of how a specific claim(s) will be adjudicated. Reimbursement is based on many factors, including member eligibility and benefits on the date of service; medical necessity; utilization management guidelines (when applicable); coordination of benefits; adherence with applicable Plan policies and procedures; clinical coding criteria; claim editing logic; and the applicable Plan – Provider agreement.