CLINICAL MEDICAL POLICY and PRIOR-AUTHORIZATION POLICY	
Policy Name:	Gene Expression Profiling in Tumor Tissue (Oncotype DX)
Policy Number:	MP-005-MD-PA
Approved By:	Medical Management
Provider Notice Date:	05/03/2016
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Revision Date:	NA
Products:	Pennsylvania Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 13

Disclaimer

Gateway Health℠ (Gateway) medical payment and prior-authorization policy is intended to serve only as a general reference resource regarding payment and coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.

POLICY STATEMENT:

Gateway Health Plan® provides coverage as a laboratory services under the medical benefits of the Company's Medicaid products for medically necessary Gene Expression Profiling diagnostic testing for breast.

The qualifications of the policy will meet the standards of the National Committee for Quality Assurance (NCQA) and the Commonwealth of Pennsylvania (PA) Department of Human Services (DHS) and all applicable state and federal regulations.

This policy is designed to address medical guidelines that are appropriate for the majority of individuals with a particular disease, illness, or condition. Each person's unique clinical circumstances warrants individual consideration, based on review of applicable medical records.

(Current applicable PA HealthChoices Agreement Section V. Program Requirements, B. Prior Authorization of Services, 1. General Prior Authorization Requirements.)

DEFINITIONS:

Prior Authorization Review Panel (PARP) — A panel of representatives from within the PA Department of Human Services who have been assigned organizational responsibility for the review, approval and denial of all PH-MCO Prior Authorization policies and procedures.

PROCEDURES

Oncotype DX™ is a diagnostic assay that quantifies the likelihood of breast cancer recurrence in women with newly diagnosed, early-stage, lymph node negative, and estrogen receptor positive (ER+) breast cancer.

1. For breast cancer to assess the need for adjuvant chemotherapy in women with recently diagnosed breast cancer when the following criteria are met:
   a) The member is a candidate for possible adjuvant chemotherapy (i.e., chemotherapy is not precluded due to other factors), and testing is being done specifically to guide the decision as to whether or not adjuvant chemotherapy will be used; AND
   b) The patient has had surgery and full pathological evaluation of the specimen has been completed (i.e., the test should not be ordered on a preliminary core biopsy); AND
   c) Primary tumor size 0.6 – 1 cm with moderate/poor differentiation or unfavorable features, OR tumor size is larger than 1 cm; AND
   d) Breast tumor is stage 1 or stage 2; AND
   e) Breast tumor is hormone receptor positive (i.e., Estrogen-Receptor Positive or progesterone positive; AND
   f) Breast tumor is HER2-receptor negative; AND
   g) There is no evidence of metastatic breast cancer, and the member is axillary-node negative; AND
   h) The laboratory and/or the ordering health care professional's documentation should indicate that the individual has cancer of the breast that is hormone receptor—positive and node-negative among meeting other clinical criteria for medically necessary testing; AND
   i) Prior to ordering the test, the ordering health care professional's documentation should indicate that the intention to treat or not treat with adjuvant chemotherapy would be contingent, at least in part, on the results of the test for the individual in question and would play a significant role in management of the individual.

Oncotype DX is not covered for conditions other than those listed above scientific evidence has not been established and are therefore considered not medically necessary. Requests for conditions not listed above will be reviewed on a case-by-case basis.

2. The following are examples of situations that are considered not medically necessary:
   1. Breast Cancer
      a) Use of Oncotype DX® to determine patient risk in patients with primary breast cancer who meet criteria above but who have already made the decision to undergo or forego chemotherapy is considered not medically necessary.

      b) The use of gene expression assays in men with breast cancer is considered not medically necessary and not covered because the safety and/or effectiveness of this service cannot be established by review of the available published peer-reviewed literature. No published literature on the use of gene expression profiling in men with breast cancer was identified.

c) Other gene expression assays for breast cancer prognosis (e.g., Mammostrat® Breast Cancer Test, the Breast Cancer Index℠, BreastOncPx™, NexCourse® Breast IHC4, Proigna™/ PAM50 Breast Cancer Intrinsic Subtype Classifier, BreastPRS™, and EnoPredict™) for any indication are considered not medically necessary and, therefore, not covered because the safety and/or effectiveness of this service cannot be established by review of the available published peer-reviewed literature.

d) Gene expression assays to molecularly subclassify breast cancer (e.g., BluePrint®) is considered not medically necessary and, therefore, not covered because the safety and/or effectiveness of this service cannot be established by review of the available published peer-reviewed literature.

e) Gene expression assays for quantitative assessment of ER, PR, and HER2 overexpression (e.g., TargetPrint®) is considered not medically necessary and, therefore, not covered because the safety and/or effectiveness of this service cannot be established by review of the available published peer-reviewed literature.

3. Colon Cancer
   a) Gene expression assays for recurrence scores in stage II and stage III colon cancer is considered not medically necessary and, therefore, not covered because the safety and/or effectiveness of this service cannot be established by review of the available published peer-reviewed literature.

4. Prostate Cancer
   a) There is no evidence is available at this time regarding whether the Oncotype DX Assay can predict the benefit of adjuvant chemotherapy in patients at risk of prostate cancer recurrence.

5) Post-payment Audit Statement
   a) The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Gateway Health Plan® at any time pursuant to the terms of your provider agreement.

6) The place of service for this testing is outpatient.

7) Governing Bodies Approval
   The Oncotype DX® tests are offered as laboratory-developed tests under Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet general regulatory standards of CLIA and must be licensed by CLIA for high complexity testing.

AUTHORIZATION and CODING REQUIREMENTS:

Oncotype DX is typically performed on an outpatient procedure and will require prior authorization. HBO treatment provided in an inpatient setting requires individual case review.

SUMMARY OF LITERATURE

For women with early stage breast cancer, adjuvant chemotherapy provides the same proportional benefit regardless of prognosis. However, the absolute benefit of chemotherapy depends on the baseline risk for recurrence. For example, women with the best prognosis have small tumors, are estrogen receptor-positive (ER+), and lymph node negative (N -). These women have an approximately 15% baseline risk of recurrence; approximately 85% of these patients would be disease-free at 10 years with tamoxifen treatment alone and could avoid the toxicity of chemotherapy if they could be accurately identified. Conventional risk classifiers estimate recurrence risk by considering criteria such as tumor size, type, grade and histologic characteristics; hormone receptor status; and lymph node status. However, no single classifier is considered a gold standard, and several common criteria have qualitative or subjective components that add variability to risk estimates. As a result, more patients are treated with chemotherapy than can benefit. Better predictors of baseline risk could help women who prefer to avoid chemotherapy if assured that their risk is low, make better treatment decisions in consultation with their physicians.

Several panels of gene expression markers ("signatures') have been identified that appear to predict the baseline risk of breast cancer recurrence after surgery, radiation therapy, and hormonal therapy (for hormone receptor-positive tumors) in women with node-negative disease. The available gene expression tests include:

- Oncotype DX® (a 21-gene RT-PCR assay; Genomic Health)
- 70-gene signature MammaPrint® (also referred to as the "Amsterdam signature"; Agendia)
- Mammostrat™ (Clarient Diagnostic Services)
- Molecular Grade Index (Aviara MGISM; AviaraDx, Inc.)
- Breast Cancer IndexSM, a combination of the Molecular Grade Index (MGI) and theHOXB13:IL17BR Index (bioTheranostics)
- BreastOncPxTM (Breast Cancer Prognosis Gene Expression Assay; LabCorp)
- Prosigna™ (NanoString Technologies)
- NexCourse® Breast IHC4 (Geneoptix)
- BreastPRS™ (Signal Genetics)
- EndoPredict™ (Sividon Diagnostics)
- BluePrint® (Agendia)
- TargetPrint® (Agendia)

Breas
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Oncotype DX Assay

The 21-Gene Recurrence Score (Oncotype DX®) assay is supported by strong evidence of clinical validity, i.e., that the recurrence score (RS) is strongly associated with risk of distant recurrence in women with invasive breast cancer that is positive for hormone receptors, negative for HER2, and without lymph node involvement. Limited but sufficient evidence supports analytic validity and clinical utility in this population. Oncotype DX® adds additional risk information to conventional clinical classification of high-risk individuals and identifies a subset of individuals who would otherwise be recommended for chemotherapy but who are actually at lower risk of recurrence (average 7% to 9% risk at 10 years; upper 95% confidence interval limits, 11% to 15%). Prior to testing, the individual and provider should discuss the potential results of the test and agree to use the results to guide therapy (i.e., the individual will forgo adjuvant chemotherapy if Oncotype DX score is low. Thus, a woman who prefers to avoid the toxicity and inconvenience of chemotherapy and whose Oncotype DX® RS value shows that she is at very low risk of

recurrence might reasonably decline chemotherapy.

In similar women who are node-positive, evidence is less clear that the risk of recurrence in low-risk RS individuals is sufficiently low or that the benefit of chemotherapy is insufficiently large, to recommend avoiding otherwise currently recommended treatment. Additional studies are necessary and ongoing. For women with ductal carcinoma in situ (DCIS), development and conductance of high-quality and robust clinical validity studies are needed to allow full evaluation of a subset of genes from the 21-gene recurrence score (i.e., Oncotype DX® DCIS) to predict recurrence and inform treatment planning post-excision. Moreover, no information is yet available on whether women are better categorized as to their recurrence risk by the Oncotype DX® DCIS Score compared with standard clinical risk indicators.

Hayes Update (2010)
The following ratings were noted by Hayes (2010):
B – For the use of the Oncotype DX assay to predict the risk of distant recurrence in women with ER+ tumors that are N–, to help in the decision regarding whether to undergo chemotherapy in addition to hormonal therapy following surgical resection.
C – For the use of the Oncotype DX assay to predict the risk of LRR in women with ER+ tumors that are N–, to help in the decision regarding whether to undergo chemotherapy in addition to hormonal therapy following surgical resection.
C – For the use of the Oncotype DX assay to predict the risk of distant recurrence in women with ER+ tumors that are N+ to help in the decision regarding whether to undergo chemotherapy in addition to hormonal therapy following
surgical resection.
C – For the use of the Oncotype DX assay to predict the magnitude of response to adjuvant chemotherapy in women with ER+ tumors that are N–.

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

Sparano et al. (2015) reported early results from the Trial Assigning Individualized Options for Treatment (TAILORx). The findings show that women with early stage hormone receptor-positive breast cancer that has a low risk of recurrence based on a test for the expression of 21 genes, five-year recurrence rates are very low when postoperative treatment consists of hormone therapy alone.

According to the Susan G. Koman breast cancer web site, Oncotype DX and ductal carcinoma in situ (DCIS) could be helpful in identifying which cases of DCIS would benefit most from radiation

therapy after lumpectomy. However, this test needs further study and is not yet part of standard practice.

There is a continued lack of evidence in the published medical literature to assess this technology and no recommendation by the NCCN at this time. For women with ductal carcinoma in situ (DCIS), studies on the use of Oncotype DX DCIS to predict recurrence and inform treatment planning post-excision have not been published. Currently available evidence is therefore insufficient to determine that Oncotype DX® DCIS improves the net health outcome in women with DCIS. Information is unavailable on whether women are better categorized as to their recurrence risk by the Oncotype DX® DCIS Score compared with standard clinical risk indicators; therefore Oncotype DX DCIS is considered investigational.

For men with primary breast cancer, studies of the utilization of Oncotype DX to determine recurrence risk for deciding whether or not to undergo adjuvant chemotherapy have not been published. No published literature on the use of gene expression profiling in men with breast cancer was identified. Further, NCCN guidelines do not address Oncotype DX utilization in men.

MammaPrint®
Based on the 2014 AHRQ Technology Assessment, there was insufficient evidence to determine the impact of MammaPrint® on treatment decisions and clinical utility, primarily due to unknown consistency and imprecision.

Breast Cancer Index℠
Currently, neither NCCN nor ASCO recommend THEROS Breast Cancer IndexSM as an option when evaluating breast cancer patients for risk of recurrence.

Molecular Grade Index (Aviara MGI℠)
Currently, neither NCCN nor ASCO recommend The Molecular Grade Index (Aviara MGISM) as an option when evaluating breast cancer patients for risk of recurrence.

Mammostrat™
Currently, neither NCCN nor ASCO recommend Mammostrat™ as an option when evaluating breast cancer patients for risk of recurrence.

BreastOncPx™
Currently, neither NCCN nor ASCO recommend Mammostrat™ as an option when evaluating breast cancer patients for risk of recurrence.

NexCourse® Breast IHC4
Currently, neither NCCN nor ASCO recommend Mammostrat™ as an option when evaluating breast cancer patients for risk of recurrence.

Prosigna™ PAM50 Breast Cancer Intrinsic Subtype Classifier
Currently, neither NCCN nor ASCO recommend Mammostrat™ as an option when evaluating breast cancer patients for risk of recurrence.

BluePrint™ and TargetPrint®
Currently, neither NCCN nor ASCO recommend Mammostrat™ as an option when evaluating breast cancer patients for risk of recurrence.

BreastPRS
Currently, neither NCCN nor ASCO recommend Mammostrat™ as an option when evaluating breast cancer patients for risk of recurrence.

EndoPredict™
Currently, neither NCCN nor ASCO recommend Mammostrat™ as an option when evaluating breast cancer patients for risk of recurrence.

Colon
According to the Genomic Health website, the Oncotype DX® colon cancer test has been validated in three prospectively-designed clinical studies involving over 3,000 patients: QUASAR, CALGB 9581 and NSABP C-07. The Quick and Simple and Reliable (QUASAR) clinical validation study (Gray, 2011) suggested that recurrence score provided a continuous measure of recurrence risk at three years. However the authors noted that there were limitations to the study which included that tumor specimens were retrieved from on 68% of the participants and the proportion of study participants with at least 12 nodes examined (38%) is lower than observed in modern clinical practice.

In the Cancer and Leukemia Group B (CALGB) 9581, Venook et al reported on a phase III clinical trial of adjuvant edrecolomab antibody therapy in individuals with surgically resected sage II colon cancer. The study population represented a group with a relatively low risk of colon cancer recurrence.

In the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 clinical trial, Yothers et al, 2013) reported on the results of this clinical validity of the Oncotype DX continuous recurrence score. Archived specimens were obtained from individuals with stage II and III colon cancer who were randomly assigned to fluorouracil (FU) or FU plus oxaliplatin. There were 892 participants, 31/264 with stage II and 214/628 with stage II colon cancer experienced recurrence of the disease. The continuous recurrence score was significantly associated with recurrence free interval (RFI).

Srivastava and colleagues (2014) carried out a multicenter prospective case series to evaluate the impact of Oncotype DX Colon recurrence score on physician recommendations for adjuvant chemotherapy for the treatment of 141 individuals with Stage II colon cancer.
The authors stated that in comparison with traditional clinicopathological assessment, the use of the recurrence score resulted in treatment modifications in 45% of the participants. There was a 30% overall reduction in adjuvant chemotherapy in this

Meanwhile, Black et al. (2012) performed a technical brief through the Agency for Healthcare Research and Quality (US) to provide a summary of the state of the science on gene expression profiling for in predicting outcomes, including benefit from adjuvant chemotherapy, in patients with stage II colon cancer. The authors reported that the available published studies on this technology did not provide data to support the clinical utility for gene expression profiling in this patient population.

The American Cancer Society (2016) noted that while there are recently developed test to predict cancer recurrence risk, none of the tests have been shown to help predict which people could benefit from chemo or other treatments.

Prostate
Gene expression profile analysis and protein biomarkers have been proposed as a means to risk-stratify patients with prostate cancer to guide treatment decisions. These tests are intended to be used either on prostate needle biopsy tissue to guide management decisions regarding active surveillance versus therapeutic intervention or post radical prostatectomy to guide radiation therapy use.

The gene expression test Oncotype DX® Prostate is intended to be used in combination with accepted clinical criteria Gleason score, prostate-specific antigen [PSA], clinical stage) to stratify biopsy-diagnosed localized prostate cancer according to biological aggressiveness and direct initial patient management.

Oncotype DX® Prostate Cancer Assay is prostate biopsy-based 17-gene RT-PCR assay, representing four molecular pathways (androgen signaling, cellular organization, stromal response and proliferation), that provides a biologic measure of cancer aggressiveness. The assay is indicated for men who are considered candidates for active surveillance (AS) (those with NCCN® very low- and low-risk prostate cancer). The assay is designed to inform decisions between AS and immediate treatment.

NCCN guidelines for prostate cancer (V1.2015) indicate that the clinical utility of Prolaris and Oncotype Dx awaits evaluation by prospective randomized clinical trials which are unlikely to be done. Currently the clinical utility of these molecular testing panels has not been fully demonstrated.

There is no evidence is available at this time regarding whether the assay can predict the benefit of adjuvant chemotherapy in patients at risk of recurrence.

REIMBURSEMENT

Participating facilities will be reimbursed per their Gateway Health Plan® contract.

POLICY SOURCE(S)

Breast
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Breast Cancer Staging

Breast cancer staging is used to determine the extent of the disease upon diagnosis. The stage of the disease is important to develop an appropriate treatment plan and determine the prognosis (expected outcome of the disease). Physical examination, imaging tests (e.g., mammogram, ultrasound), and pathology results following biopsy or other surgery are used to stage breast cancer.

Stage 0

Stage 0 breast cancer sometimes is considered a pre-cancerous condition. Ductal carcinoma in situ (DCIS) is an example of stage 0 breast cancer. In DCIS, cancer cells are located within a milk duct, but have not invaded breast tissue or spread to lymph nodes or distant sites. Other types of breast cancer that may be classified as stage 0 include lobular carcinoma in situ (LCIS) and Paget disease of the nipple.

Stage I

In stage I breast cancer, the tumor is 2 cm or less in diameter (T1) and cancer cells have not

spread to lymph nodes (N0) or to distant sites (M0).

Stage II

Stage II breast cancer is classified as stage IIA or stage IIB. A stage IIA classification involves the following:

- No tumor is located in the breast (T0), but cancer cells are found in 1–3 axillary (under the arm) lymph nodes (N1) and have not spread to distant sites (M0); or
- Tumor is less than 2 cm in diameter (T1) and cancer cells have spread to 1–3 axillary lymph nodes (N1), but not spread to distant sites (M0); or
- Tumor is larger than 2 cm and less than 5 cm in diameter (T2) and cancer cells have not spread to axillary nodes (N0) or to distant sites (M0).

Stage IIB classification of breast cancer involves the following:

- Tumor is larger than 2 cm and less than 5 cm in diameter (T2) and cancer cells have spread to 1–3 axillary lymph nodes (N1), but not spread to distant sites (M0); or
- Tumor is larger than 5 cm and does not grow into the chest wall (T3) and cancer cells have not spread to lymph nodes (N0) or to distant sites (M0).

Breast cancer also is classified as stage IIB when sentinel node biopsy, but not imaging tests or clinical examination, shows that cancer cells have spread to internal mammary lymph nodes.

Stage III

Classifications for stage III breast cancer include stage IIIA, stage IIIB, and stage IIIC. Stage IIIA involves the following:

- Tumor is less than 5 cm in diameter (T0–T2) and cancer cells have spread to 4 to 9 axillary lymph nodes (N2), but not spread to distant sites (M0); or
- Tumor is larger than 5 cm (T3) and cancer cells have spread to 1 to 9 axillary nodes (N0–N2) or to internal mammary nodes, but not spread to distant sites (M0).

In stage IIIB breast cancer, the tumor has grown into the chest wall or the skin (T4) and cancer cells may have spread to as many as 9 axillary nodes (N0–N2), but not spread to distant sites (M0).

Diagnosis Codes

ICD-10 Code	Description
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.19	Malignant neoplasm of nipple and areola, unspecified female breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.119	Malignant neoplasm of central portion of unspecified female breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.219	Malignant neoplasm of upper-inner quadrant of unspecified female breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast

C50.319	Malignant neoplasm of lower-inner quadrant of unspecified female breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.619	Malignant neoplasm of axillary tail of unspecified female breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast
Z17.0	Estrogen receptor positive status [ER+]

Procedure Codes

CPT Code	Description
81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as a 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, and algorithm reported as a recurrence score
81479	Unlisted molecular pathology procedure