HIGHMARK Delaware
HEALTH OPTIONS

CLINICAL MEDICAL POLICY	
Policy Name:	Gene Expression Profiling in Tumor Tissue (Oncotype DX)
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Products:	Highmark Health Options Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 15

DISCLAIMER

Highmark Health Options medical policy is intended to serve only as a general reference resource regarding 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

Highmark Health Options may provide coverage as a laboratory service under its medical benefits of the Company's Medicaid products for medically necessary Gene Expression Profiling diagnostic testing for breast cancer.

Genetic testing coverage is provided when the information is needed to adequately assess risk in the Highmark Health Options member, and the information is expected to make an impact on the member's treatment plan or the responsible family member/legal guardian intends to use the information in making decisions about his/her care or treatment plan.

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

The qualifications of the policy will meet the standards of the National Committee for Quality Assurance (NCQA) and the Delaware Department of Health and Social Services (DHSS) and all applicable state and federal regulations.

DEFINITIONS

Adjuvant Chemotherapy – Adjuvant means additional. Adjuvant chemotherapy is given to patients after primary treatment (e.g., chemotherapy and radiation, or chemotherapy and surgery) when the doctor thinks there is a high risk the cancer will return. Adjuvant chemotherapy aims to destroy hidden cancer cells that remain but are undetectable.

HER2/neu or HER2 - A protein cell surface receptor that controls signals to other cells to direct growth, division or repairs.

Node Negative – Indicates that the cancer has not spread to the lymph nodes (micro metastases smaller than 2.0mm in aggregate that are included with node-negative for purposes [pN1mi]).

Oncotype DX Recurrence Score Assay – Is a genetic assay of 21 genes (16 cancer genes of interest and 5 reference genes) used to quantify the risk of distance recurrence and the likelihood of chemotherapy benefit in patients with certain types of newly diagnosed early stage node-negative breast cancer.

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 men or women with recently diagnosed breast cancer when the following criteria are met:
   A. The patient 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–>.5 1 cm with moderate/poor differentiation or unfavorable features, OR tumor size is larger than 1 cm; AND
   D. Breast tumor is stage I or stage II, unilateral and non-fixed; 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 patient is axillary-node negative; (lymph nodes with micrometastases which are <2mm in size are considered node negative) AND
   H. The laboratory's 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; AND
   J. No previous Oncotype DX testing on the same sample when a result was successfully obtained; AND
   K. No previous gene expression assay has been performed on the same sample with satisfactory results.

Note: For unusual circumstances, such as test failure or testing two separate breast cancers, individual consideration by a Medical Director review is required.

2. Oncotype DX is not covered for conditions other than those listed above because 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. The following are examples of situations that are considered not medically necessary:
    A. Breast Cancer
        1) The use of Oncotype DX to determine patient risk in patients with primary breast cancer who meet the criteria above but have already made the decision to undergo or forego chemotherapy is considered not medically necessary; OR
        2) 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; OR
        3) Repeat Oncotype DX testing is considered not medically necessary when a result was successfully obtained; OR
        4) Other gene expression assays for breast cancer prognosis (e.g., Mammostrat® Breast Cancer Test, MammaPrint®, the Breast Cancer Index^{SM}, BreastOncPx™, NexCourse® Breast IHC4, Proigna™/ PAM50 Breast Cancer Intrinsic Subtype Classifier, BreastPRS™, Oncotype DX ® DCIS and EndoPredict™) 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.
        5) Gene expression assays to molecularly subclassify breast cancer (e.g., BluePrint®) 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.
        6) Gene expression assays for quantitative assessment of ER, PR, and HER2 overexpression (e.g., TargetPrint®) 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.

    B. Colon Cancer
        Gene expression assays for recurrence scores in stage II and stage III colon cancer 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.

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

3. Post-payment Audit Statement
    The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Health Options at any time pursuant to the terms of your provider agreement.

4. Place of Service
   The place of service for this testing is outpatient.

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.

CODING REQUIREMENTS

Procedure Codes

Breast

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
0008M	Oncology (breast), mRNA analysis of 58 genes using hybrid capture, on formalin-fixed paraffin-embedded (FFPE) tissue, prognostic algorithm reported as a risk score

Prostate (Noncovered)

CPT Codes	Description
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
81551	Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy
0011M	Oncology, prostate cancer, mRNA expression assay of 12 genes (10 content and 2 housekeeping), RT-PCR testy utilizing blood plasma and/or urine, algorithms to predict high-grade prostate cancer
0005U	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score
0047U	Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score

Colon (Noncovered)

CPT Code	Description
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

Note: Requests for any for the noncovered codes listed above require review by a Medical Director for medical necessity review.

Diagnosis Codes for Procedures 81519 & 0008M

ICD-10 Codes	Description
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.021	Malignant neoplasm of nipple and areola, right male breast
C50.022	Malignant neoplasm of nipple and areola, left male breast
C50.029	Malignant neoplasm of nipple and areola, unspecified male 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
C50.121	Malignant neoplasm of central portion of right male breast
C50.122	Malignant neoplasm of central portion of left male breast
C50.129	Malignant neoplasm of central portion of unspecified male 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
C50.221	Malignant neoplasm of upper-inner quadrant of right male breast
C50.222	Malignant neoplasm of upper-inner quadrant of left male breast
C50.229	Malignant neoplasm of upper-inner quadrant of unspecified male 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
C50.321	Malignant neoplasm of lower-inner quadrant of right male breast
C50.322	Malignant neoplasm of lower-inner quadrant of left male breast
C50.329	Malignant neoplasm of lower-inner quadrant of unspecified male 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
C50.421	Malignant neoplasm of upper-outer quadrant of right male breast
C50.422	Malignant neoplasm of upper-outer quadrant of left male breast
C50.429	Malignant neoplasm of upper-outer quadrant of unspecified male 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
C50.521	Malignant neoplasm of lower-outer quadrant of right male breast
C50.522	Malignant neoplasm of lower-outer quadrant of left male breast
C50.529	Malignant neoplasm of lower-outer quadrant of unspecified male 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
C50.621	Malignant neoplasm of axillary tail of right male breast
C50.622	Malignant neoplasm of axillary tail of left male breast

C50.629	Malignant neoplasm of axillary tail of unspecified male 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
C50.821	Malignant neoplasm of overlapping sites of right male breast
C50.822	Malignant neoplasm of overlapping sites of left male breast
C50.829	Malignant neoplasm of overlapping sites of unspecified male 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
C50.921	Malignant neoplasm of unspecified site of right male breast
C50.922	Malignant neoplasm of unspecified site of left male breast
C50.929	Malignant neoplasm of unspecified site of unspecified male breast
Z17.0	Estrogen receptor positive status [ER+]

REIMBURSEMENT

Participating facilities will be reimbursed per their Highmark Health Options contract.

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 to 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)

Breast Cancer

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-.

Razaq et al. (2016) reported on the use of gene expression profiling as a treatment strategy in male breast cancer. The report summarized available literature and case series on the use of Oncotype DX in male breast cancer. While breast cancer is typically identified with women, the disease does occur in men. However, treatment for men is normally extrapolated from the experience in the female population. In The authors noted that there was not much literature available in study of men but reviewed as American Society of Clinical Oncology (ASCO) poster by Genomic health in 2009. The study reviewed 347 male breast cancer samples along with 82,000 female breast cancer samples using Oncotype DX. The results demonstrated that male breast cancer displays similar gene signatures to female breast cancer. The authors concluded that Oncotype DX can be a good tool to determine therapeutic strategy in male breast cancer patients just as in female breast cancer patients in the evaluation of benefiting from adjuvant chemotherapy as well as avoidance of chemotherapy toxicity in over treatment of patients.

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.

The American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the AHRQ Technology Assessment have been evaluated for clinical positions and guidelines on the biomarkers to guide the decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer. Please see the following recommendations:

- MammaPrint®
  In 2016, the American Society of Clinical Oncology (ASCO) released a clinical practice guideline on use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage

invasive breast cancer. The ASCO does not recommend the use of MammaPrint assays for women to guide decisions on adjuvant systemic chemotherapy in the following prognoses:

- ER/PgR-positive, HER2-negative breast cancer; OR
- HER2-positive breast cancer; OR
- TN breast cancer

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℠ (BCI)
  Currently, the NCCN does not recommend THEROS Breast Cancer Index℠ as an option when evaluating breast cancer patients for risk of recurrence.

  The 2017 ASCO clinical practice guidelines recommend the Breast Cancer Index biomarker tests as an option be used in guiding decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer.

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

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

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

- NexCourse® Breast IHC4
  Currently, the NCCN nor ASCO recommends NexCourse Breast IHC4 as an option when evaluating breast cancer patients for risk of recurrence.

- Prosigna™ PAM50 Breast Cancer Intrinsic Subtype Classifier
  Currently, the NCCN does not recommend Prosigna as an option when evaluating breast cancer patients for risk of recurrence.

  The 2017 ASCO clinical practice guidelines recommend Prosigna as an option when evaluating patients with ER/PgR-positive, HER-2 negative (node negative) breast cancer, in conjunction with other clinicopathologic variables, to guide decisions on adjuvant systemic therapy.

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

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

- EndoPredict™
  Currently, NCCN does not recommend EndoPredict as an option when evaluating breast cancer patients for risk of recurrence.

  The 2017 ASCO clinical practice guidelines recommend the EndoPredict biomarker tests as an option be used in guiding decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer.

Colon Cancer

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 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 Stage 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 III 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 receiving adjuvant chemotherapy following review of the recurrence score between the physician and the participant.

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 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 tests to predict cancer recurrence risk, none of the tests have been shown to help predict which people could benefit from chemotherapy or other treatments.

Prostate Cancer

Gene expression profile analysis and protein biomarkers have been proposed as 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 on 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 a 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 available at this time regarding whether the assay can predict the benefit of adjuvant chemotherapy in patients at risk of recurrence.

POLICY SOURCE(S)

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Policy History

Date	Activity
06/07/2016	QI/UM Committee approval
12/01/2016	Provider effective date
03/14/2017	Format changes; Page 1-Added Related Policy Number; Page 3-Changed Operational Guidelines from postservice to preservice; Page 4- added Policy History box; several areas reworded for clarification; Page 11-added description for Stage IIIC breast cancer; updated the disclaimer on page 1; updated formatting throughout document;
08/09/2017	Added Disclaimer Statement in opening of medical policy. EHS Revisions: Added Issue Date to opening policy box; Added 'Covered' to Procedure and Diagnosis Code Tables; Added 'Informational' to Attachment D; Procedure code 81479 duplicated in MP-013-MD-DE; updated Operational Guidelines to address procedure and diagnosis code matching for claims processing. Corrected typographic error for ICD-10 code C50.19 to C50.019.
12/14/2017	Annual Review: Added a definition; Added non-coverage indications to #2; reformatted procedure section and summary of literature to meet current societal recommendations; added references
03/13/2018	QI/UM Committee Review Approval
05/15/2018	Provider Effective Date
12/11/2018	Annual Revision: Removed the word 'Covered' from the procedure and diagnosis code tables in Attachments B & C: Under the Procedure code section, added men as eligible; corrected noncovered section to remove the male exclusion and added appropriate ICD-10 diagnosis for males in Table C; Under Attachment B, deleted procedure code 81479 and added 0008M in the first table for breast cancer, created two noncovered procedure code tables to separate prostate (81541, 81551, 0011M, 0005U & 0047U) and colon cancer (81525); updated Summary of Literature; deleted hyperlinks from all references; additional references included
12/11/2018	QI/UM Committee Review
02/18/2019	Provider Effective Date