CLINICAL MEDICAL POLICY	
Policy Name:	Gene Expression Testing for Cancer Treatment (Breast, Colon, Prostate)
Policy Number:	MP-005-MD-PA
Responsible Department(s):	Medical Management
Provider Notice/Issue Date:	11/01/2023; 11/01/2022; 12/17/2022; 11/23/2020; 12/09/2019; 12/15/2018; 04/15/2018; 07/05/2016
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Products:	Highmark Wholecare℠ Medicaid
Application:	All participating hospitals and providers
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Policy History

Date	Activity
12/01/2023	Provider Effective date
10/23/2023	PARP Approval
09/20/2023	QI/UM Committee review
09/20/2023	Annual Review: No changes to clinical criteria. Updated 'Summary of Literature' and 'Reference Sources' sections.
12/01/2022	Provider Effective date
10/11/2022	PARP Approval
09/21/2022	QI/UM Committee review
09/21/2022	Annual Review: Policy name changed from "Gene Expression Testing for Breast Cancer Treatment" to "Gene Expression Testing for Cancer Treatment (Breast, Colon, Prostate)" to account for colon and prostate cancer. No changes to clinical criteria. Removed the word "covered" and replaced with "not medically necessary". Updated 'Summary of Literature' and 'Reference Sources' sections. Updated the code description for CPT code 81519. Removed deleted CPT code 0008M; replaced with new code 81520. Removed the following unspecified ICD-10 codes: C50.019, C50.029, C50.119, C50.129, C50.219, C50.229, C50.319, C50.329, C50.419, C50.429, C50.519, C50.529, C50.619, C50.629, C50.819, C50.829, C50.919, & C50.929.

01/17/2022	Provider effective date
11/30/2021	PARP Approval
09/15/2021	QI/UM Committee review
09/15/2021	Annual Review: Changes made to Procedures section medical necessity guidelines, and formatting. Updated Summary of Literature and Reference Sources sections.
12/21/2020	Provider effective date
11/10/2020	PARP approval
09/16/2020	QI/UM Committee review
09/16/2020	Annual Review; changed Policy Title from "Gene Expression Profiling in Tumor Tissue (Oncotype DX®)". Updated Prostate Cancer section under Procedures to include "experimental and investigational", updated Summary of Literature
12/09/2019	Provider Effective Date
10/24/2019	PARP Approval
09/18/2019	QI/UM Committee Review
09/18/2019	Annual Review: Added 2 definitions for colon cancer and prostate cancer gene expression profiling; removed the 'not medically necessary' statements in Procedure section 2 and replaced with experimental and investigational statement; Added 0045U –ductal carcinoma in situ to the noncovered procedure code table
12/15/2018	Provider Effective Date

Disclaimer

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

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 warrant individual consideration, based on review of applicable medical records.

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.

(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 Pennsylvania 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.

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.

Oncotype DX Colon Cancer Assay - A reverse transcription PCR (RT-PCR)-based profiling test (by Genomic Health Inc.) that measure 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 2 or stage 3 colon cancer. A proprietary algorithm is used to calculate a recurrence score that quantifies patient risk for colon cancer recurrence.

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.

Procedures

1. Highmark Wholecare℠ will provide coverage for gene expression testing (Oncotype DX) in individuals with recently diagnosed breast cancer when ALL of the following criteria are met:
   A. The individual 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. Prior to ordering the test, the ordering health care professional's documentation indicates that the intention to treat or not treat with adjuvant chemotherapy would be contingent, at least in part, on the results of the test and would play a significant role in management of the individual; AND
   C. The individual 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
   D. The breast tumor is hormone receptor positive (i.e., Estrogen-Receptor Positive or progesterone positive); AND
   E. ANY ONE of the following is present:
      1) The primary tumor size is between 0.5 – 1 cm with moderate/poor differentiation or unfavorable features, OR
      2) The tumor size is larger than 1 cm and is HER2-receptor negative; AND
   F. The breast tumor is stage 1 or stage 2; AND
   G. There is no evidence of metastatic breast cancer; AND
   H. ANY ONE of the following is present:
      1) the individual is axillary-node negative (lymph nodes with micro metastases which are <2mm in size are considered node negative), OR
      2) 1-3 positive lymph nodes.; AND
   I. There has been no previous Oncotype DX testing on the same sample when a result was successfully obtained; AND
   J. 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 for two separate breast cancers, individual consideration by a Medical Director review is required.

2. Gene expression testing is considered not medically necessary for conditions other than those listed above because scientific evidence has not been established. Requests for conditions not listed above will be reviewed by a Medical Director on a case-by-case basis. The following are examples of situations that are considered experimental and investigational, and therefore are not medically necessary:
   A. For breast cancer:
      - The use of Oncotype DX to determine risk in individuals with primary breast cancer who meet the criteria listed above but have already made the decision to undergo, or forego, chemotherapy.
      - Repeat Oncotype DX testing when a result has been successfully obtained.
      - A gene expression assay has been performed on the same sample with satisfactory results.
      - Other gene expression assays for breast cancer prognosis (e.g., Mammostrat® Breast Cancer Test, MammaPrint®, the Breast Cancer Index℠, BreastOncPx™, NexCourse®

Breast IHC4, Proigna™/ PAM50 Breast Cancer Intrinsic Subtype Classifier, BreastPRS™, Oncotype DX DCIS® and EndoPredict™) for any indication because the safety and/or effectiveness of this service cannot be established by review of the available published peer-reviewed literature.

- Gene expression assays to molecularly subclassify breast cancer (e.g., BluePrint®) because the safety and/or effectiveness of this service cannot be established by review of the available published peer-reviewed literature.
- Gene expression assays for quantitative assessment of ER, PR, and HER2 overexpression (e.g., TargetPrint®) because the safety and/or effectiveness of this service cannot be established by review of the available published peer-reviewed literature.

B. For colon cancer:
- Gene expression assays for recurrence scores in stage II and stage III colon cancer is considered experimental and investigational because the safety and/or effectiveness of this service cannot be established by review of the available published peer-reviewed literature.

C. For prostate cancer:
- There is no evidence available at this time regarding whether a gene expression assay can predict the benefit of adjuvant chemotherapy in patients at risk of prostate cancer recurrence, and is therefore considered experimental and investigational.

3. Place of Service

The proper place of service for gene expression testing is outpatient.

4. Post-payment Audit Statement

The medical record should include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Wholecare℠ at any time pursuant to the terms of your provider agreement.

5. Related Policies

- MP-074-MD-PA Oncologic Genetic Testing Panels
- MP-011-MD-PA BRCA 1 & 2 Genetic Mutation Testing and Related Genetic Counseling
- MP-059-MD-PA Colorectal Cancer Screening
- MP-100-MD-PA Gene Expression and Biomarker Prostate Cancer Testing

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.

The Centers for Medicare and Medicaid Services (CMS) has published the following guidance:

The following Local Coverage Articles (LCA) have been published by CMS:

- National Coverage Determination Prostate Cancer Screening Tests (210.1) (The use of Oncotype genomic prostate score [GPS] assays is not discussed in the NCD)
- Billing and Coding: MolDX: Oncotype DX® Breast Cancer Assay (A55230)
- Billing and Coding: MolDX: Oncotype DX® Breast Cancer for DCIS (Genomic Health™) (A57583)
- Billing and Coding: MolDX: Oncotype DX® Colon Cancer Assay Update (A55231)

Summary of Literature

Breast Cancer

Breast cancer is the most common cancer in women in the United States, except for skin cancers. It is about 30% of all new female cancers each year. Approximately 287,850 new cases of invasive breast cancer will be diagnosed in women in 2022. Breast cancer usually occurs in middle-aged and older women. The median age at the time of breast cancer diagnosis is 62. This means half of the women who developed breast cancer are 62 years of age or younger when they are diagnosed. A very small number of women diagnosed with breast cancer are younger than 45 (ACS, 2022).

The most commonly used breast imaging tests currently used are mammograms, ultrasound, and breast MRI. Other tests, such as CT scans, bone scans, or PET scans might sometimes be done to help to detect if breast cancer has spread. If the results of these tests suggest a patient has breast cancer then a biopsy may be performed to confirm the findings. During the biopsy, the suspicious tissue is removed from the breast. Gene expression testing is performed on breast cancer cells after a biopsy to examine patterns of a number of different genes (ACS, 2022).

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 patients 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)

According to the American Cancer Society, only the Oncotype Dx® breast cancer assay has been shown to help predict which patients benefit the most from certain treatments (ACS, 2014).

- **Oncotype DX® Assay**
  Oncotype DX is a diagnostic assay that quantifies the likelihood of distant breast cancer recurrence in women with newly diagnosed, early stage breast cancer. The assay is performed using formalin-fixed, paraffin-embedded (FFPE) tumor tissue and analyzes the expression of a panel of 21 genes that were selected through analysis of three different clinical trial cohorts. The results are provided as a Recurrence Score (RS) measured on a scale of 0 to 100 with a RS of 17 being low risk; 18 to 30 being intermediate risk, and more than 30 being high risk. Among the genes assessed by the assay, the proliferation and estrogen receptor (ER) pathways and HER-2 expression have the greatest impact on the RS calculation (Fowble, Melisko, 2010).

  The American Society of Clinical Oncology (ASCO) has recommended Oncotype DX to guide decisions for adjuvant endocrine and chemotherapy for a patient who has been diagnosed with node-negative breast cancer (ASCO, 2022).

  According to the National Comprehensive Cancer Network (NCCN), Oncotype Dx is preferred by the NCCN Breast Cancer Panel for prognosis and prediction of chemotherapy benefit. The 21-gene recurrence score (RS) is one of the most validated multigene assays (NCCN, 2022).

  The 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” (NCCN, 2022).

  Hayes, Inc.
- <u>Oncotype DX Breast Recurrence Score (Genomic Health Inc.) for Lymph Node–Positive Patients</u>
  For patients with N1, ER+, HER2– invasive breast cancer, there is limited evidence to suggest that the Oncotype DX test may estimate the risk of distant recurrence (prognosis) and the likely benefit of chemotherapy (prediction) in order to guide effective treatment decisions for patients. The limited but consistent evidence is supportive of the prognostic ability. The identified study did not report consistent results to support the predictive ability. The Oncotype Dx test results may

change patient management, but the studies did not report if the changes were resulted in improved health outcomes. However, by inference, the Oncotype DX test may improve immediate outcomes by decreasing the total number of patients treated with chemotherapy, thus avoiding the harms of treatment.

For patients with N2, ER+, HER2–, invasive breast cancer, there is insufficient evidence that use of the Oncotype DX test estimates the risk of distant recurrence (prognosis) and the likely benefit of chemotherapy (prediction) in order to guide effective treatment decisions, largely due to the limited numbers of studies identified by the search criteria for this report.

- **C Rating** – For the use of the Oncotype DX Breast Recurrence Score (Oncotype DX) test as a prognostic indicator for 9-year distant breast cancer recurrence for patients diagnosed with estrogen receptor–positive (ER+), human epidermal growth factor 2–negative (HER2–), and N1 invasive breast cancer.
- **D2 Rating** – For the use of the Oncotype DX test as a predictive indicator for the likelihood of chemotherapy benefit for patients diagnosed with ER+, HER2–, and N1 invasive breast cancer.
- **D2 Rating** – For the use of the Oncotype DX test as a prognostic indicator for 9-year distant breast cancer recurrence for patients diagnosed with ER+, HER2–, and N2 invasive breast cancer.
- **D2 Rating** - For the use of the Oncotype DX test as a predictive indicator for the likelihood of chemotherapy benefit for patients diagnosed with ER+, HER2–, and N2 invasive breast cancer.

- <u>Oncotype DX Breast Recurrence Score for Lymph Node–Negative Patients (Genomic Health Inc.)</u>
  For patients with N–, ER+, HER2– invasive breast cancer, the evidence suggests that the Oncotype DX test estimates the risk of distant recurrence (prognosis) and the likely benefit of chemotherapy (prediction) in order to guide effective treatment decisions for patients diagnosed with ER+, HER2– invasive breast cancer. Questions remain regarding the RS range necessary to predict the likelihood of chemotherapy benefit in subgroup populations. Additional clinical utility studies are needed that report the follow-up of health outcomes after the RS-based treatment recommendation.
  - **B Rating** - For the use of the Oncotype DX Breast Recurrence Score test as a prognostic indicator for 9-year distant breast cancer recurrence for patients diagnosed with estrogen receptor–positive (ER+), human epidermal growth factor 2–negative (HER2–), and node-negative (N– or N0) invasive breast cancer.
  - **C Rating** - For the use of the Oncotype DX Breast Recurrence Score test as a predictive indicator for the likelihood of chemotherapy benefit for patients diagnosed with ER+, HER2–, and N– invasive breast cancer.

- <u>Oncotype DX Breast DCIS Score (Genomic Health Inc.)</u>
  There is positive but insufficient evidence supporting the use of the Oncotype DX Breast DCIS Score. Additional studies are needed in different and less selective populations to support the premise that the DCIS Score provides a prediction for 10-year local recurrence and establishes a baseline for consideration of absolute benefit from radiation therapy. Available studies do not evaluate whether the test results, when used to influence patient risk assessment and medical management selection, result in improved patient outcomes, such as avoiding adverse effects of unnecessary treatment without undertreatment.

- **D2 Rating** - For the use of Oncotype DX Breast DCIS Score: (1) as a prognostic indicator of 10-year local (ductal carcinoma in situ [DCIS] or invasive carcinoma) recurrence or invasive local recurrence; and (2) to establish a baseline consideration for radiation therapy benefit in women diagnosed with DCIS.

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. 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.

According to the Susan G. Komen 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 patients 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 patients 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.

Wang et al., (2019) conducted a study which evaluated the prognostic significance of the Oncotype DX recurrence score (RS) in T1-2N1M0 estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer. The Surveillance, Epidemiology, and End Results database was searched to identify ER-positive invasive ductal breast cancer in T1-2N1M0 with RS results diagnosed between 2004 and 2012. Patients with RS were categorized into low-risk (RS < 11), intermediate-risk (RS 11–25), and high-risk (RS > 25) groups. The study enrolled 4059 cases categorized into prognostic stages IA to IIB. The RS risk groups differed significantly in terms of breast cancer severity score (BCSS) and OS ($P < 0.001$). According to the multivariate analysis, RS risk group was an independent prognostic factor for BCSS and OS together with the pathological prognostic stage. The subgroup analysis showed similar survival rates across pathological prognostic stages in the RS low-risk group but significant differences in survival rates among pathological prognostic stages in the RS intermediate-risk group. The survival rates among the RS risk groups also differed significantly in pathological prognostic stage IA. Oncotype DX RS provided independent prognostic significance to complement the prognostic staging system.

In similar patients 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 patients 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 patients are better categorized as to their recurrence risk by the Oncotype DX DCIS Score compared with standard clinical risk indicators.

Sparano et al. (2015) reported early results from the Trial Assigning Individualized Options for Treatment (TAILORx). The findings show that patients with early stage hormone receptor-positive breast cancer that has have 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.

- **MammaPrint®**
  The ASCO recommends the following in regards to the use of MammaPrint:
  - If a patient is older than 50 and has high clinical risk breast cancer, that is node-negative or node-positive with 1-3 positive nodes, the clinician may use MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy
  - If a patient is 50 years of age or younger and has high clinical risk, node-negative or node-positive with 1-3 positive nodes breast cancer, the clinician should not use the MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy.
  - If a patient has low clinical risk, regardless of age, the evidence on clinical utility of routine MammaPrint test is insufficient to recommend its use (ASCO, 2022).

  The NCCN noted that the results from the randomized MINDACT trial demonstrated that the 70-gene assay (MammaPrint) can identify a subset of patients who have a low likelihood of distant recurrence despite high-risk clinical features (based on tumor size, grade, nodal status, etc) (NCCN, 2022).

- **Breast Cancer Index℠ (BCI)**
  The Breast Cancer Index (BCI) is a combination of two profiles, the HOXB13-to-IL17BR expression ratio (H:I ratio) and the Molecular Grade Index (MGI). . There are limited data as to the role of BCI in HR-positive, HER2-negative, and lymph node-positive breast cancer (NCCN, 2022).

  The ASCO recommends the following:
  - If a patient has node-negative or node-positive with 1-3 positive nodes breast cancer and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, the clinician may offer BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI or a sequence of tamoxifen followed by AI.
  - If a patient has node-positive breast cancer with more than 3 positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, there is insufficient evidence to use BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI or a sequence of tamoxifen followed by AI (ASCO, 2022).

- **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, neither 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 ASCO clinical practice guidelines state that if a patient is premenopausal, and has node-negative or node-positive breast cancer, the clinician should not use the Prosigna test to guide decisions for adjuvant systemic chemotherapy (ASCO, 2022).

- **BluePrint™ and TargetPrint®**
  Neither the 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 ASCO recommends the following:
  - If a patient is postmenopausal and has breast cancer that is node-negative or node-positive with 1-3 positive nodes, the clinician may use EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy.
  - If a patient is premenopausal and has breast cancer that is node-negative or node-positive with 1-3 positive nodes, the clinician should not use EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy.
  - If a patient has breast cancer with more than 3 positive nodes, evidence on the clinical utility of routine use of EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy is insufficient (ASCO, 2022).

Hayes, Inc.

- <u>EndoPredict (Myriad Genetics Laboratories Inc.)</u>
  There is limited but positive evidence to suggest that EPclin, calculated by the EndoPredict test, may estimate the 10-year risk of DR in patients with ER+, HER2−, N0, early-stage breast cancer. Whether the test can prospectively distinguish low-risk patients from others and whether the test is equally applicable to premenopausal women remain unclear.

There is insufficient but positive evidence to suggest that the EndoPredict test may estimate the 10-year risk of DR in patients with ER+, HER2−, N1, early-stage breast cancer. The evidence is limited by the number of studies and data. There were conflicting results as to whether the EPclin low-risk group was truly associated with low risk (< 10%) of DR in this group of patients.

There is insufficient evidence to support the use of the EndoPredict test to estimate the likelihood of DR 5 to 15 years from diagnosis and the absolute benefit of chemotherapy at 10 years in patients with ER+, HER2−, N0/N1, early-stage breast cancer. These conclusions are due to the limited number of studies and data to support these test results.

In this report, clinical validity studies were analyses of previously conducted clinical trials based in Europe. No prospectively designed studies were identified. Additional studies are needed, such as well-powered prospective studies to examine diverse patient demographics and potentially improved patient outcomes resulting from the EndoPredict test.

- **C Rating** - For use of the EndoPredict test to estimate the risk of distant recurrence (DR) for years 0 to 10 in patients diagnosed with estrogen receptor–positive (ER+), human epidermal growth factor receptor 2–negative (HER2−), node-negative, early-stage breast cancer
- **D2 Rating** - For use of the EndoPredict test to estimate the risk of DR for years 0 to 10 in patients diagnosed with ER+, HER2−, node-positive (1-3 positive lymph nodes), early-stage breast cancer
- **D2 Rating** - For use of the EndoPredict test to estimate the likelihood of DR 5 to 15 years after diagnosis in patients with ER+, HER2−, early-stage breast cancer
- **D2 Rating** - For use of the EndoPredict test to estimate the absolute benefit of chemotherapy at 10 years in patients with ER+, HER2−, early-stage breast cancer

Colon Cancer

Excluding skin cancers, colorectal cancer is the third most common cancer diagnosed in the United States. The rate of people being diagnosed with colon or rectal cancer each year has dropped overall since the mid-1980s, mainly because more people are getting screened and changing their lifestyle-related risk factors (ACS, 2022).

Several assays have been developed in hopes of providing prognostic and predictive information to aid in decisions regarding adjuvant therapy in patients with stage II or III colon cancer, including Oncotype DX, ColoPrint, and ColDX. The NCCN guidelines provides that the information from these tests can further inform the risk of recurrence over other risk factors, but the panel questions the value added. Furthermore, evidence of predictive value in terms of the potential benefit of chemotherapy is lacking. Therefore, the panel believes that there are insufficient data to recommend the use of multigene assays (NCCN, 2022).

Hayes, Inc.

- Oncotype DX Colon Recurrence Score test (Genomic Health Inc.)
  - **D2 Rating** - For use of the Oncotype DX Colon Recurrence Score test for risk of recurrence in stage II, mismatch repair proficient (MMR-P) colon cancer patients using formalin-fixed paraffin-embedded (FFPE) tumor specimens.
  - **D2 Rating** - For use of the Oncotype DX Colon Recurrence Score test for risk of recurrence in stage IIIA/B colon cancer patients using FFPE tumor specimens.

The evidence to support the Oncotype DX Colon Recurrence Score test's analytical validity, clinical validity, and clinical utility for estimating recurrence risk in patients with anatomic stage II, MMR-P or stage IIIA/B colon cancers who have undergone surgical resection but not started chemotherapy or other treatment is insufficient.

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 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 (Gray, 2011).

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.

Prostate Cancer

Other than skin cancer, prostate cancer is the most common cancer in American men. Prostate cancer is more likely to develop in older men and in non-Hispanic Black men. About 6 cases in 10 are diagnosed in men who are 65 or older, and it is rare in men under 40. The average age of men at diagnosis is about 66 (ACS, 2022).

The ASCO guidelines recommend the following in regards to gene expression testing for prostate cancer:

- Commercially available molecular biomarkers (ie, Oncotype Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with

routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended.
- Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Eggener, Rumble, Armstrong, et al., 2020).

The NCCN recommends the following regarding molecular assays:
- Men with low or favorable intermediate-risk disease and life expectancy >10 y may consider the use of the following tumor-based assays: Decipher, Oncotype DX Prostate, Prolaris, and ProMark. Men with unfavorable intermediate- and high-risk disease and life expectancy >10 y may consider the use of Decipher and Prolaris tumor-based molecular assays.
- Molecular biomarker tests have been developed with extensive industry support, guidance, and involvement, and have been marketed under the less rigorous FDA regulatory pathways for biomarkers. Although full assessment of their clinical utility requires prospective randomized clinical trials, which are unlikely to be done, the panel believes that men with low or favorable intermediate disease may consider the use of Decipher, Oncotype DX Prostate, Prolaris, or ProMark during initial risk stratification (NCCN, 2022).

Hayes, Inc.
- Oncotype DX Genomic Prostate Score (GPS) Assay (Genomic Health Inc.)
  - **C Rating** - For use of the Oncotype DX Genomic Prostate Score (GPS) assay to help make treatment decisions by accurately predicting: (1) likelihood of adverse pathology; (2) risk of prostate cancer death within 10 years; and (3) risk of metastasis within 10 years in men with newly diagnosed, localized prostate cancer meeting National Comprehensive Cancer Network very low, low, or favorable intermediate-risk criteria who are eligible for active surveillance.

    The evidence to support the analytical validity, clinical validity, and clinical utility of the Oncotype DX GPS assay is insufficient. Available studies do not evaluate whether the test results, when used to influence patient risk assessment and medical management selection, result in improved patient outcomes such as avoidance of adverse effects of unnecessary treatment without undertreatment of progressive disease.

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 recurrence score
81520	Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score
0045U	Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by real-hyphentime RT-hyphenPCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score

Prostate (Noncovered)
Requests for any of the noncovered codes listed below require a medical necessity review by a Medical Director.

CPT Code	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 urine, algorithms to predict high-grade prostate cancer risk
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

Diagnosis Codes for Procedures **81519, 81520** & **0045U** :

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
C50.021	Malignant neoplasm of nipple and areola, right male breast
C50.022	Malignant neoplasm of nipple and areola, left male breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.121	Malignant neoplasm of central portion of right male breast
C50.122	Malignant neoplasm of central portion of left 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
C50.221	Malignant neoplasm of upper-inner quadrant of right male breast
C50.222	Malignant neoplasm of upper-inner quadrant of left 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
C50.321	Malignant neoplasm of lower-inner quadrant of right male breast
C50.322	Malignant neoplasm of lower-inner quadrant of left 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
C50.421	Malignant neoplasm of upper-outer quadrant of right male breast
C50.422	Malignant neoplasm of upper-outer quadrant of left 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
C50.521	Malignant neoplasm of lower-outer quadrant of right male breast
C50.522	Malignant neoplasm of lower-outer quadrant of left male breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.621	Malignant neoplasm of axillary tail of right male breast
C50.622	Malignant neoplasm of axillary tail of left male breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.821	Malignant neoplasm of overlapping sites of right male breast
C50.822	Malignant neoplasm of overlapping sites of left male breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.921	Malignant neoplasm of unspecified site of right male breast
C50.922	Malignant neoplasm of unspecified site of left male breast
Z17.0	Estrogen receptor positive status [ER+]

Informational

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

Describes invasive breast cancer (cancer cells are breaking through to or invading normal surrounding breast tissue). Divided into subcategories IA and IB.

- Stage IA describes invasive breast cancer in which:
  - The tumor measures up to 2 centimeters and
  - The cancer has not spread outside the breast; no lymph nodes are involved
- Stage IB describes invasive breast cancer in which:
  - There is no tumor in the breast; instead, small groups of cancer cells – larger than 0.2 mm but not larger than 2 mm – are found in the lymph nodes or
  - There is a tumor in the breast that is no larger than 2 cm, and there are small groups of cancer cells – larger than 0.2 mm but not larger than 2 mm – in the lymph nodes

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

- 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 to distant sites (M0).
- Stage IIIC breast cancer, there may be no sign of cancer in the breast or, if there is a tumor, it may be any size and may have spread to the chest wall and/or the skin of the breast; and the cancer has spread to 10 or more axillary lymph nodes, or the cancer has spread to lymph nodes above or below the collarbone; or the cancer has spread to axillary lymph nodes or lymph nodes near the breastbone.

Stage IV

Stage IV describes invasive breast cancer that has spread beyond the breast and nearby lymph nodes to other organs of the body, such as the lungs, distant lymph nodes, skin, bones, liver or brain.

Reimbursement

Participating facilities will be reimbursed per their Highmark Wholecare℠ contract.

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