CLINICAL MEDICAL POLICY	
Policy Name:	Gene Expression and Biomarker Prostate Cancer Testing
Policy Number:	MP-100-MD-PA
Responsible Department(s):	Medical Management
Provider Notice/Issue Date:	10/01/2023; 10/01/2022; 12/17/2021; 11/16/2020; 12/09/2019; 05/20/2019
Effective Date:	11/01/2023; 11/01/2022; 01/17/2022; 12/21/2020; 12/09/2019; 05/20/2019
Next Annual Review:	08/2024
Revision Date:	08/16/2023; 08/17/2022; 08/18/2021; 08/19/2020; 08/01/2019
Products:	Highmark Wholecare℠ Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 9

Policy History

Date	Activity
11/01/2023	Provider Effective date
09/21/2023	PARP Approval
08/16/2023	QI/UM Committee review
08/16/2023	Annual Review: No changes to experimental/investigational status. Updated 'Summary of Literature' and 'Reference Sources' sections.
11/01/2022	Provider Effective date
09/09/2022	PARP Approval
08/17/2022	QI/UM Committee review
08/17/2022	Annual Review: No changes to clinical criteria. Changed policy title from "*Prostate Cancer Testing*", to "*Gene Expression and Biomarker Prostate Cancer Testing*". Removed 'Limitations' section, as all procedures mentioned in this policy are considered experimental/investigational. Removed CMS-specific coverage guidelines. Updated 'Summary of Literature' and 'Reference Sources' sections.
01/17/2022	Provider effective date
11/30/2021	PARP Approval
08/18/2021	QI/UM Committee review
08/18/2021	Annual Review: No changes to clinical criteria. Added TAG determination information and Program Exception statement. Updated Summary of Literature and Reference Sources sections.

01/02/2019	Initial policy developed

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 ℠ does not provide coverage under the medical-surgical benefits of the Company's Medicaid products for prostate cancer testing.

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.

(Current applicable Pennsylvania 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.

Prolaris™ - A prognostic genetic test developed by Myriad that measures tumor cell growth from prostate biopsy cores or prostatectomy tissue. It is an array-based test that is used to quantify expression levels of 46 cell cycle progression (CCP) genes and 15 housekeeper genes to generate a cell-cycle progression score (Prolaris score). The Prolaris test score paired with prostate-specific antigen (PSA) and Gleason grade reportedly provides a level of aggressiveness of an individual with prostate cancer.

PCA3 - Prostate cancer antigen 3 testing is an FDA-approved urine biomarker assay that measures the levels of prostate cancer gene 3. This gene is found in high levels in prostate cancer cells.

4Kscore - The 4Kscore test measures blood levels of four Kallikreins protein biomarkers (total prostate-specific antigen [PSA], free PSA [fPSA], intact PSA [iPSA], and human Kallikrein-related peptidase 2 [hK2]) in addition to other clinical information, including age, digital rectal examination (DRE), and prior biopsy history. All of these components are placed into a proprietary algorithm to provide a percent risk for a high-grade Gleason score greater than or equal to 7 cancer on biopsy. The 4Kscore test algorithm's goal is to refine patient selection for biopsies to reduce unnecessary biopsies in men being considered for biopsy of the prostate for potential cancer.

Procedures

1. Highmark Wholecare considers the use of prognostic genetic tests (Prolaris), prostate cancer antigen 3 testing (PCA3) and/or 4Kscore protein biomarkers to detect prostate cancer to be experimental/investigational and not medically necessary for any indications.

2. Post-payment Audit Statement
   The medical record must 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.

3. Place of Service
   The proper place of service for prostate cancer testing can be either the inpatient or outpatient setting.

4. Related Policies
   - MP-005-MD-PA Gene Expression Profiling in Tumor Tissue (Oncotype DX®)
   - MP-101-MD-PA Repetitive Transcranial Magnetic Stimulation
   - MP-074-MD-PA Oncologic Genetic Testing Panels

Operational Guidelines *Do not include on external version*

- This medical policy will be applied on a preservice, prepayment basis for both facility and professional providers.
- Claims for this services mentioned in the Coding Requirements section below are considered not medically necessary and should be denied as experimental/investigational.

Governing Bodies Approval

On February 13, 2012, the FDA approved the Progensa PCA2 Assay. The approval was indicated for use in conjunction with other patient information to aid in the decision for repeat biopsy in men 50 years of age or older who have had one or more previous negative prostate biopsies and for whom a repeat biopsy would be recommended by a urologist based on current standard of care, before consideration of Progensa PCA3 assay results. A PCA3 score < 25 is associated with a decreased likelihood of a positive biopsy. Prostatic biopsy is required for diagnosis of cancer.

To date, the FDA has chosen to not require regulatory review of testing that is available under the auspices of Clinical Laboratory Improvement Amendments (CLIA). The Prolaris test is offered as laboratory-developed tests under 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 Prolaris testing is an example of a proprietary genetic test (Myriad).

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

- National Coverage Determination (NCD) Prostate Cancer Screening Tests (210.1)
- Local Coverage Determination (LCD) 4Kscore Test Algorithm (L37792)

The Pennsylvania Department of Human Services Technology Assessment Group (TAG) workgroup meets quarterly to discuss issues revolving around new technologies and technologies or services that were previously considered to be a program exception. During this meeting, decisions are made as to whether or not certain technologies will be covered and how they will be covered. TAG's decisions are as follow:

- Option #1: Approved - Will be added to the Fee Schedule
- Option #2: Approved as Medically Effective - Will require Program Exception
- Option #3: Approved with (or denied due to) Limited/Minimal Evidence of Effectiveness - Will require Program Exception
- Option #4: Denied - Experimental/Investigational

In August 2015, the TAG workgroup assigned PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ration (e.g., prostate cancer) an Option #4, specifically for CPT code 81313.

In August 2018, the TAG workgroup assigned Polaris Prostate Cancer Test an Option #4, specifically for CPT code 81541.

In May, 2023, the TAG workgroup reviewed the 4K Score Test an Option #4 ranking and determined the Option #4 was still appropriate, specifically for CPT 81539.

Summary of Literature

It is estimated that 248,530 new cases of prostate cancer will have been diagnosed in 2021. Furthermore, researchers have estimated that prostate cancer will account for nearly 10.7% of male cancer deaths in 2021. Per the American Cancer Society, prostate cancer develops mainly in older men and in non-Hispanic black men. Approximately six cases in ten are diagnosed in men aged 65 or older, and it is rare before the age of 40. However, prostate cancer can be a serious disease, but most men diagnosed with prostate cancer do not die from it. More than 3.1 million men in the United States who have been diagnosed with prostate cancer at some point are still alive today (NCCN, 2023).

Prostate cancer can be a highly variable and heterogeneous disease, making diagnosis, prognosis and treatment a challenging risk. With an increasing number of aging men in the population at risk for the disease, there are significant implications of these biopsy and subsequent treatment decisions. Since multiple biomarker tests currently exist with many more in development, it may be difficult for clinicians to decide on which test to use. Current challenges in the management of prostate cancer include the risk assessment, providing early and accurate detection, monitoring of low-risk patients who are under surveillance only, predicting recurrence after initial treatment, and assessing efficacy of treatment. In order to address these needs, several tests have been developed (Uhr, Glick, Gomella, 2020).

According to the Agency for Healthcare Research and Quality (AHRQ), there is no standard screening test for prostate cancer. Researchers are studying different tests to find those with the fewest risks and most benefits. Prostate cancer screening has risks:

- Finding prostate cancer may not improve your health or help you live longer
- The results can sometimes be wrong
- Follow-up tests, such as a biopsy, may have complications

The healthcare provider should discuss with the patient the risks for prostate cancer, the pros and cons of the screening tests, and whether the test are medically necessary.

Two tests are commonly used to screen for prostate cancer:

- A prostate-specific antigen test, also called a PSA blood test. PSA is a protein made by the prostate. A high level of PSA in an individual's blood may mean they have prostate cancer, but it's not proof of cancer. That's because many other things may cause high PSA levels, including:
    - Having an enlarged prostate (benign prostatic hyperplasia or BPH)
    - Having other common prostate problems
    - Taking certain medicines

  In general, the higher an individual's PSA, the more likely it is that they have cancer. But a low PSA blood level is not a guarantee that an individual does not have cancer.
- Digital Rectal Examination (DRE) is an exam in which the health care provider inserts a lubricated, gloved finger into the patient's rectum to feel the prostate for lumps or anything unusual. A DRE can check only one side of the prostate.

A PSA test or a DRE may be able to detect prostate cancer at an early stage. But it is not clear whether early detection and treatment lower the risk of dying from prostate cancer. Individuals should talk with their provider about the benefits and harms of prostate cancer screening (MedLinePlus, 2022).

The NCCN guidelines for prostate cancer state that men with very low risk, low risk, and favorable intermediate-risk prostate cancer, with at least ten years' life expectancy, who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy, may consider the use of the following tumor-based molecular assays: Decipher, Oncotype DX Prostate, and Prolaris. Retrospective studies have shown that molecular assays performed on prostate biopsy or radical prostatectomy specimens provide prognostic information independent of the NCCN risk groups. These include, but are not limited to, likelihood of death with conservative management, likelihood of biochemical progression after radical prostatectomy or external beam therapy, and likelihood of developing metastasis after radical prostatectomy or salvage radiotherapy. The Discussion section notes that the clinical utility has not been established in prospective random controlled clinical trials or comparative effectiveness studies (NCCN, 2023).

The NCCN panel recommends consideration of biomarker tests that have been validated in peer-reviewed, multi-site studies using an independent cohort of patients. These include percent free PSA (%f PSA), which may improve cancer detection and Prostate Health Index (PHI), Select MDx, 4Kscore, or ExoDx Prostate Test (EPI), which may further define the probability of Grade Group > cancer in patients with PSA levels >3 ng/mL who have not yet had a biopsy. %f PSA, PHI, 4Kscore, EPI, PCA3, and ConfirmMDx may also be considered for those who have had at least one prior negative biopsy and are thought to be at higher risk. The extent of validation of these test across diverse population varies. Results of biomarker assays can be complex and should be interpreted with caution. Referral to a specialist should be considered (NCCN, 2023).

Prognostic methods have been developed due to the need for risk stratification in prostate cancer. Two examples of microarray-based gene expression profiles are Prolaris and Oncotype DX Prostate Cancer Assays that utilize prostate biopsy samples. When the scores from either exam are combined in proprietary algorithms with clinical risk criteria (PSA, Gleason grade and tumor stage), it has been reported that the results will reflect a biological indolence or aggressiveness of individual lesion, and therefore inform management decisions.

The American Association of Clinical Urologists (AACU) issued a position statement on genomic testing for prostate cancer that supports coverage of tissue–based molecular testing as a component of risk stratification used in prostate cancer treatment decision-making. The AACU also strongly encourages taking family cancer histories and pursuing germline testing where appropriate to provide patients and their families with clarity about their hereditary cancer risk. They also support ongoing research to further refine the prognostic power of these tests.

The American Urological Association (AUA), American Society for Radiation Oncology (ASTRO), and the Society of Urologic Oncology (SUO) position statement states that among most low-risk localized prostate cancer patients, tissue-based genomic biomarkers have not shown a clear role in the selection of candidates for active surveillance.

4Kscore

The 4Kscore Test is a non-FDA approved blood test that provides a patient-specific probability for finding an aggressive (Gleason score 7 or higher) prostate cancer upon biopsy. The information can be used by the urologist to have an informed discussion with the patient about whether or not to have a prostate biopsy. The 4Kscore Test measures four prostate-specific kallikrein in the blood: Total PSA, Free PSA, Intact PSA, and Human Kallikrein 2 (hK2). The blood test results are combined in an algorithm with patient age, digital rectal exam (nodule, no nodule), and prior negative biopsy (yes, no). The 4Kscore Test then provides a percentage probability on a scale from < 1% to > 95% for the patient having aggressive prostate cancer.

The NCCN panel consensus is that the test can be considered for patients prior to biopsy and for those with prior negative biopsy who are thought to be at higher risk for clinically significant prostate cancer. It is important for patients and their urologists to understand, however, that no optimal cut-off threshold has been established for the 4kscore. If a 4kscore test is performed, the patient and his urologist should discuss the results to decide whether to proceed with a biopsy (NCCN, 2023).

A Hayes, Inc. report focused on the analytical validity, clinical validity, and clinical utility of the 4Kscore Test to aid in prostate cancer biopsy decision making for physician and patient through: (1) estimating a patient's percentage of risk for aggressive (Gleason ≥ 7) prostate cancer if a prostate biopsy were performed; and (2) providing information on the 10-year likelihood of developing distant metastases when the 4Kscore result is < 7.5%. The 4Kscore test was given a '**D2**' rating by Hayes. There is insufficient evidence supporting the use of the 4Kscore Test to aid in prostate cancer biopsy decision making for physician and patient (Hayes, 2022).

PCA3

The prostate cancer antigen 3 gene (PCA3) test is used to help determine a person's risk of developing prostate cancer, it is not used to diagnose prostate cancer. PCA3 is used to determine a patient's elevated prostate-specific antigen (PSA) levels are likely caused by prostate cancer. PSA is a protein produced by cells in the prostate. Elevated levels of this protein could indicate a harmless problem with the prostate, such as an enlarged prostate. However, elevated PSA levels can also indicate prostate cancer. The PCA3 test can help to identify a genetic marker in the urine. If the genetic marker and elevated PSA levels are in the body, the elevated levels are more likely to be caused by prostate cancer than by another condition. (Marcin & Morris, 2017).

PCA3 is a gene that exists in all prostate gland cells. It causes these cells to make small amounts of certain proteins, it is also present in urine. Prostate cells that are cancerous can make 60-100 times more of this protein than noncancerous cells. When this occurs, the extra proteins will also leak into the urine. If the

PCA3 test detects this protein in the urine, this may signal that prostate cancer is present (Luo & Galan, 2019).

At the cellular level, PCA3 determination can separate benign from malignant prostate cells with an accuracy approaching 100%. PCA3 transcripts have been detected in a wide range of human extraprostatic benign and cancerous tissues, indicating that PCA3 is the most specific prostate cancer gene identified to date. Overexpression of PCA3 by cancer cells has allowed diagnostic use of gene levels in tissues or fluids containing prostate cellular material (Marks & Bostwick, 2008).

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group found insufficient evidence to recommend PCA3 testing to inform decisions for when to rebiopsy previously biopsy-negative patients for prostate cancer or to inform decisions to conduct initial biopsies for prostate cancer in at-risk men (e.g., previous elevated prostate-specific antigen test or suspicious digital rectal examination). The EGAPP found insufficient evidence to recommend PCA3 testing in men with cancer-positive biopsies to determine if the disease is indolent or aggressive in order to develop an optimal treatment plan. EGAPP found that based on the available evidence, the overall certainty of net health benefit for PCA3 testing is deemed "low." The Evaluation of Genomic Applications in Practice and Prevention Working Group discourages clinical use unless further evidence supports improved clinical outcomes (CDC, 2016).

The NCCN panel believes the PCA3 test is not appropriate to use in the initial biopsy setting (NCCN, 2023).

Prolaris

Prolaris is a genomic test that analyzes changes in 46 genes in prostate biopsy tissue. It generates a risk score to help predict the likelihood of disease progression in men with localized prostate cancer. Prolaris is intended to guide the decision regarding active surveillance without surgery or radiation for low- or intermediate-grade cancers vs. active treatment with immediate surgery or radiation therapy (Ebell, 2019). This test can also be useful in post prostatectomy specimens to predict 10 year risk of biochemical recurrence to help identify patients who may benefit from adjuvant therapy (Uhr, Glick, Gomella, 2020).

Future comparative effectiveness research may allow the Prolaris test and others like it to gain additional evidence regarding their utility for better risk stratification of patients with prostate cancer (NCCN, 2023).

A Hayes molecular test assessment maintained a '**D2**' rating for the use of Prolaris Biopsy for determining the 10-year risk of both metastatic disease after definitive therapy and disease-specific mortality if conservatively managed. It was determined that there is insufficient evidence to support Prolaris Biopsy test as available studies do not provide direct evidence that the test drives decision making nor reported subsequent clinical outcomes (Hayes, 2022).

Coding Requirements

Non-covered Procedure Codes
These procedure codes will not be reimbursed without Medical Director Approval.

CPT Code	Description
81313	PCA3/KLK3 (prostate cancer antigen 3 [non-hyphenprotein coding]/kallikrein-hyphenrelated peptidase 3 [prostate specific antigen]) ratio (e.g., prostate cancer)
81539	Oncology (high-hyphengrade prostate cancer), biochemical assay of four proteins (Total PSA, Free PSA, Intact PSA, and human kallikrein-hyphen2 [hK2]), utilizing plasma or serum, prognostic algorithm reported as a probability score
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

Reimbursement

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

Reference Sources

Myriad Genetics. Prolaris: A Prognostic Medicine Product for Prostate Cancer. Accessed on July 13, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 2.2023. July 17, 2023. Accessed on August 2, 2023.

National Comprehensive Cancer Network (NCCN). Prostate Cancer Early Detection. Version 1.2023. January 9, 2023. Accessed on August 2, 2023.

American Association of Clinical Urologists, Inc. (AACU). Position statement: genomic testing in prostate cancer. Accessed on July 16, 2021.

Sanda MG, Cadeddu JA, Kirkby E, et al. Clinical localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: risk stratification, shared decision making and care options. Journal of Urology. March 2018. Accessed on July 16, 2021.

American Cancer Society. Prostate Cancer: Early detection, diagnosis and staging. Accessed on July 16, 2021.

Pennsylvania Department of Human Services. Technology Assessment Group (TAG) Coverage Decisions. Managed Care Operations Memorandum OPS #8/2016-009. Accessed on July 28, 2022.

Pennsylvania Department of Human Services. Technology Assessment Group Coverage (TAG) Decisions. Managed Care Operations Memorandum OPS # 05/2023-002. 4Kscore test. February 8, 2023. Accessed on May 8, 2023.

Pennsylvania Department of Human Services. Technology Assessment Group (TAG) Coverage Decisions. Managed Care Operations Memorandum OPS #08-2015-009. PCA/KLK3. Accessed on July 28, 2022.

U. S. Food and Drug Administration Premarket Notification Database. PRIGENSA®PCA3 assay: Summary of safety and effectiveness. Premarket Approval Application (PMA) number P100033. February 13, 2012. Accessed on July 16, 2021.

Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD) 4Kscore Test Algorithm (L37792). Original effective date March 21, 2019. Revision date December 30, 2019. Accessed on August 2, 2023.

Centers for Medicare and Medicaid Services (CMS). National Coverage Determination (NCD) Prostate Cancer Screening Tests (210.1). Effective date June 19, 2006. Implementation date June 19, 2006. Accessed on August 2, 2023.

Agency for Healthcare Research and Quality (AHRQ). Effective Health Care Program: Prostate Cancer Screening. Accessed on August 2, 2023.

Hayes, Inc. Molecular Test Assessment: 4Kscore Test (OPKO Health Inc.). June 19, 2019. Annual Review February 11, 2022. Accessed on August 2, 2023.

Hayes, Inc. Molecular Test Assessment: Prolaris Biopsy Test (Myriad Genetic Laboratories, Inc). April 19, 2019. Annual Review February 14, 2022. Accessed on August 2, 2023.

Ebell MH. Prolaris Test for Prostate Cancer Risk Assessment. Am Fam Physician. September 2019. Accessed on July 13, 2021.

Uhr A, Glick L, Gomella L. An overview of biomarkers in the diagnosis and management of prostate cancer. Can J Urol. 2020. Accessed on July 13, 2021.

Marcin J, Morris SY. What Is a PCA3 Test? Healthline. April 13, 2017. Accessed on July 28, 2022.

Luo EK, Galan N. All you need to know about the PCA3 test. Medical News Today. October 14, 2019. Accessed on July 28, 2022.

Marks LS, Bostwick DG. Prostate Cancer Specificity of PCA3 Gene Testing: Examples from Clinical Practice. Reviews in Urology. 2008. Accessed on July 28, 2022.

Centers for Disease Control and Prevention (CDC). The Evaluation of Genomic Applications in Practice and Prevention Working Group. Does PCA3 Testing for the Diagnosis and Management of Prostate Cancer improve patient health outcomes? November 18, 2016. Accessed on July 28, 2022.

MedLinePlus. Prostate Cancer Screening. March 29, 2022. Accessed on August 2, 2023.