Protein Biomarker and Genetic Testing for the Prostate

MEDICAL POLICY NUMBER: 96

Effective Date: 7/1/2026

Last Review Date: 4/2026

Next Annual Review: 4/2027

COVERAGE CRITERIA 2
POLICY CROSS REFERENCES 4
POLICY GUIDELINES 4
REGULATORY STATUS 9
CLINICAL EVIDENCE AND LITERATURE REVIEW 10
HEALTH EQUITY CONSIDERATIONS 20
BILLING GUIDELINES AND CODING 20
REFERENCES 22
POLICY REVISION HISTORY 25

INSTRUCTIONS FOR USE: Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

SCOPE: Providence Health Plan, Providence Health Assurance and Providence Plan Partners as applicable (referred to individually as "Company" and collectively as "Companies").

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☐ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

PHA members must meet the testing criteria governed by the Oregon Health Plan (OHP) - OHP Diagnostic Procedure Codes / Procedure Group 1119. Diagnostic services needed to establish a diagnosis are covered regardless of where the ultimate diagnosis appears. Once the diagnosis is determined, coverage of further treatment is reimbursed if the service appears funded by the OHA for that condition. Medicaid members must also meet the genetic testing criteria governed by the Oregon Health Plan (OHP) Prioritized List Guideline Notes D1 and D17.

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

Medically Necessary

Note: Tests listed in Criteria I, II, and III have been validated by National Comprehensive Cancer Network (NCCN) guidelines as a category 1 or 2A recommendation for prostate cancer.

I. Decipher Prostate, Oncotype DX Genomic Prostate Score Assay, and Prolaris Molecular Assay may be considered **medically necessary** for the treatment of prostate cancer patients when any of the following criteria are met (A.-C.):

   A. Life expectancy is at least 10 years and patient has any of the following prostate cancer risk types (1.-4):
      1. Low risk;
      2. Favorable intermediate risk;
      3. Unfavorable intermediate risk;
      4. High risk; **or**
   B. Adverse features were identified after radical prostatectomy (i.e. positive margin(s), seminal vesicle invasion, extracapsular extension, or detectable PSA); **or**

C. Suspicion of recurrent prostate cancer as evidenced by newly-elevated PSA following radical prostatectomy**.**

II. Prior to initial prostate biopsy, the following biomarker tests may be considered **medically necessary** to better define the probability of high-grade cancer (Grade Group ≥2):
    A. Prostate Health Index (PHI)
    B. SelectMDx
    C. 4Kscore
    D. ExoDx Prostate test
    E. MyProstateScore (MPS)
    F. MPS 2.0 (MPS2)
    G. Stockholm3
    H. IsoPSA

III. After initial prostate biopsy, the following biomarker tests may be considered **medically necessary** for members who are thought to be high risk despite a negative prostate biopsy:
    A. Prostate Health Index (PHI)
    B. percent-free PSA
    C. 4Kscore
    D. ConfirmMDx
    E. ExoDX Prostate Test
    F. MyProstateScore (MPS)
    G. MPS 2.0 (MPS2)
    H. IsoPSA

Not Medically Necessary

IV. Androgen receptor splice variant 7 (AR-V7) testing from circulating tumor cells (e.g., Oncotype DX® AR-V7 Nucleus Detect Test) is considered **not medically necessary.**

V. Repeat testing of the same germline genetic content, for the same genetic information, is considered **not medically necessary**.

VI. The use of molecular assays, including protein biomarkers and genetic testing is considered **not medically necessary** for screening, detection, diagnosis and management of prostate cancer when the above criteria are not met or when the tests are not recommended by NCCN guidelines. These assays include, but are not limited to the following:

    A. APIFINY® Score
    B. ClarityDx Prostate, Protean BioDiagnostics
    C. EpiScore
    D. EpiSwitch® Prostate Screening Test (PSE), Oxford BioDynamics Inc
    E. miR Sentinel Prostate Cancer Test, miR Scientific
    F. NeoLAB Prostate Liquid Biopsy
    G. PanGIA Prostate
    H. Progensa® PCA3 Assay
    I. ProMark

J. ProstTAV, Life Length S.L
K. PROSTOX™ ultra, MiraDx, Inc.
L. UroSeq®

Link to Evidence Summary

POLICY CROSS REFERENCES

- Circulating Tumor Cell and DNA Assays for Cancer Management, MP122
- Non-Covered Genetic Panel Tests, MP213

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

DOCUMENTATION REQUIREMENTS

In order to determine the clinical utility of a genetic test, the following documentation must be provided at the time of the request. Failure to submit complete documentation may affect the outcome of the review.

- Specific gene, trade or proprietary name of the test, or if a custom-built test, include every gene(s) and/or component of the test
- Name of laboratory where the testing is being conducted or was conducted
- Clinical notes to include the following:
  - Documentation of genetic counseling as required in the policy criteria below which includes how test results will impact clinical decision making
  - Reason (indication) for performing test, including the suspected condition
  - Existing signs and/or symptoms related to reason for current test request
  - Prior test/laboratory results related to reason for current test request
  - Family history, if applicable
  - How results from current test request will impact clinical decision making
- All relevant CPT/HCPCS codes billed

BACKGROUND

Prostate Cancer

In the United States, prostate cancer is the second most common cancer (after skin cancers) in men. Approximately 1 in 9 men will be diagnosed with prostate cancer in his lifetime, and it is more common in older men and men of African American ethnicity. In 2018, it is estimated that 164,690 men will be diagnosed with prostate cancer and 29,430 will die of the disease in the United States.[1]

Although almost all prostate cancers are adenocarcinomas, there are several other types of prostate cancer, including sarcomas, small cell carcinomas, neuroendocrine tumors and transitional cell

carcinomas.[1] Prostate cancer is a heterogeneous disease with tumors ranging from indolent to very aggressive. Survival differs according to disease stage at diagnosis. The majority of prostate cancers are discovered prior to becoming metastatic and therefore the 5-year relative survival rate is close to 100%. However, men with metastatic disease have a 5-year survival rate of approximately 30%.[2]

Prostate Cancer Detection

Prostate cancer is commonly identified in asymptomatic men by routine screening that includes measuring levels of prostate-specific antigen (PSA) in blood and via digital rectal examination (DRE). When initial testing results are suspicious for prostate cancer, a 12-core prostate biopsy is typically performed using a transrectal ultrasound (TRUS).[3]

Although biopsy is considered the standard to diagnose prostate cancer, 20-30% may yield false negative results due, in part, to poor tissue sampling during biopsy that has missed localized lesions. As a result, a large proportion of patients with an initial negative biopsy may undergo repeat biopsy if there is a suspicion of prostate cancer based on other clinical factors. Therefore, confirming the presence or absence of prostate cancer, as well as discriminating indolent from aggressive disease, are areas of research and clinical interest.[4] To address this need, a variety of blood- and urine-based protein biomarker and genetic tests are currently being developed in an attempt to provide additional information for identifying high-risk patients who may require treatment, as well as low-risk patients who may forego biopsy.

Prognosis and Treatment Decisions

Once a patient receives a diagnosis of prostate cancer, decisions about treatment are based on several factors including: tumor grade, disease stage, and predictions about the future behavior of the tumor, patient age, general health, and preferences.[5] Elevated PSA in the blood and tumor grade measured by histopathological analysis are two common prognostic indicators considered when making treatment decisions. However, elevated PSA levels may also indicate certain benign conditions. More recently, new genetic tests performed on prostate tissue samples are proposed to aid in stratifying patients according to prostate cancer aggressiveness and aid in treatment decisions.

New molecular assays include protein biomarker quantification and several different types of genetic tests, including DNA methylation assays and RNA-based expression assays. Examples of available prostate cancer molecular assays are as follows:

Molecular Assays for Prostate Cancer Detection

4Kscore Test (OPKO)

According to the manufacturer, the 4Kscore Test assays four prostate-specific kallikrein proteins (total PSA, free PSA, intact PSA and hK2) from blood and combines these results with clinical components (prior biopsy status, age and DRE) in an algorithm that calculates the individual patient's percent risk for aggressive prostate cancer. The 4Kscore can be used prior to biopsy, or after a negative biopsy and may predict the probability of distant metastasis.

The test is intended to be used as a supplement to aid in the decision of whether or not to perform a biopsy and should not be used in isolation as a stand-alone test. The company does not recommend a percent risk generated by the 4Kscore test by which to base decisions on, but indicates that the physician select their own risk level and integrate it in with other information (health status, medical history, family history of prostate cancer, PSA history, etc.) to make decisions regarding prostate biopsy.

The test is not indicated in men with:

- "With a previous diagnosis of prostate cancer
- That is younger than 40 or older than 80 years of age
- That has received a DRE in the previous 96 hours (4 days) before phlebotomy. A DRE performed after the phlebotomy is acceptable
- That has received 5-alpha reductase inhibitor (5-ARI) therapy, such as Avodart® (dutasteride) or Proscar® (finasteride), within the previous six (6) months
- That has undergone any procedure or therapy to treat symptomatic BPH or any invasive, urologic procedure that may be associated with a secondary PSA elevation prior to phlebotomy within the previous six (6) months

ConfirmMDx Test (MDxHealth)

ConfirmMDx is a polymerase chain reaction (PCR)-based genetic test that quantifies DNA methylation on the promoters of three prostate cancer –associated genes (GSTP1, APC and RASSF1) using core biopsy formalin-fixed, paraffin-embedded (FFPE) tissue samples. This assay is intended "to aid in the detection of occult prostate cancer on previously biopsied, histopathologically negative tissue."[6]

EpiScore

EpiScore is an algorithm that quantifies the relative DNA methylation intensities of the same three genes as the ConfirmMDx tests described above (GSTP1, RASSF1, and APC) from prostate biopsy tissue. The test is proposed as a method to compensate for biopsy under-sampling and improve risk stratification at the time of diagnosis. This test may help in early detection of aggressive prostate cancer.[7]

ExoDx Prostate (also known as IntelliScore) (Exosome Diagnostics)

ExoDx Prostate is a urine-based assay that extracts RNA extract from exosomes, which are microvesicles that are released from their cell of origin into the urine. The assay measures the RNA expression of three genes (PCA3, ERG, and SPDEF) and is designed to be used along with PSA and other factors (age, race and family history) to help enable physicians to predict whether a patient presenting for an initial biopsy does not have high-grade prostate cancer (Gleason grade 7 and higher) and could potentially avoid an initial biopsy. It is intended for use in patients older than 50 years of age with no prior biopsy and PSA levels between 2-10ng/ml.

Mi-Prostate score (also known as Michigan Prostate Score or MIPS) (MLabs, University of Michigan)

The Mi-Prostate score assay is a two-sample assay that combines total serum PSA and urine-based expression of the PCA3 gene and the TMPRSS2:ENG fusion gene (thought to be a genetic alteration thought occurs early in prostate cancer development).[3] According to the test lab website, the test is intended to be used as an "adjunct to serum prostate specific antigen (PSA) for risk stratification of

patients undergoing prostate biopsy. MiPS incorporates serum PSA, urine PCA3 score, and urine TMPRSS2:ERG score in logistic regression models to derive scores giving the risk of detecting prostate cancer and the risk of detecting high grade (Gleason score >6) prostate cancer on diagnostic needle biopsy.

NeoLAB Prostate Liquid Biopsy (NeoGenomics Laboratories, Inc.)

The NeoLAB Prostate test is a quantitative real time PCR (qRT-PCR) test designed to look at expression levels of 12 genes associated with prostate cancer in urine and plasma samples. The expression levels of these genes are then used in two proprietary algorithms to determine a patient's cancer risk. The manufacturer of the test claims that "NeoLAB Prostate differentiates non-cancer and low-risk cancers from high-risk prostate cancer, reducing the need for unnecessary biopsies."[8]

PanGIA Prostate (Genetic Institute of America)

PanGIA Prostate is a is a multi-analyte urine assay with algorithmic analysis that estimates an individual's risk of having prostate cancer. The test is marketed as a method to examine if a patient should undergo a prostate biopsy. Currently, there is a lack of evidence on the clinical value of the PanGIA Prostate.

Progensa® PCA3 Assay (Hologic, Inc.)

The Progensa PCA3 assay is post-DRE urine-based genetic test that measures the levels of prostate cancer antigen 3 (PCA3), which is a prostate-specific noncoding RNA that is overexpressed in a high proportion of prostate cancer cases. The assay generates a PCA3 score, which is used to estimate the probability of having a positive repeat biopsy.[4]

The test is intended to help clinicians identify patients at low risk of cancer who may forego repeat prostate biopsy in favor of clinical surveillance. The test is indicated for patients 50 years of age or older who have had one or more negative prostate biopsies, but who may be at risk for prostate cancer based on other clinical factors. The test is "to be used in conjunction with serum PSA and other risk indicators to guide appropriate patient management in the 'at risk' population of men for whom a repeat biopsy would be recommended based on current standard of care." The Progensa PCA3 Assay is not indicated for patients with atypical small acinar proliferation on their most recent biopsy.[4]

Prostate Health Index (PHI)(Beckman Coulter)

According to the manufacturer, the PHI is a diagnostic multivariate index calculated by combining the results of three different assays quantitating three forms of PSA, from blood collected prior to the DRE. The three assays measure PSA, free or unbound PSA, and p2PSA (an isoform of free PSA). The three protein biomarker levels are combined using a specific formula to calculate the PHI.[2]

The PHI is intended to aid in distinguishing prostate cancer from benign prostatic conditions in men aged 50 years and older with normal DRE findings. In the United States, the PHI is indicated for men with PSA levels between 4-10ng/mL.[2]

Although low PHI scores are thought to be associated with a lower probability of prostate cancer on biopsy, the manufacturer does not provide a specific PHI score to use as a cutoff for biopsy decision. Instead, the manufacture indicates that the cut-off PHI for biopsy decision may vary for each patient and depend on other clinical factors or family history.

SelectMDx Test (MDxHealth)

SelectMDx is a quantitative, multiplex, reverse transcription polymerase chain reaction (RT-PCR) assay performed on urine collected after a digital rectal exam that measures the expression of two genes associated with prostate cancer aggressiveness, DLX1 and HOXC6.[3] This is non-invasive assay is also referred to as a "liquid biopsy".

SelectMDx is indicated for patients with clinical risk factors for prostate cancer (e.g., elevated PSA levels and urinary symptoms). It is intended to help clinicians evaluate a patient's risk of aggressive prostate cancer and therefore help identify individuals who should undergo prostate biopsy. The test is intended to allow low-risk patients to avoid unnecessary prostate biopsy and the associated risks.[9]

Molecular Assays for Prognosis or Treatment

Decipher (GenomeDx)

According to the manufacturer, the Decipher test is a genetic test that measures the expression levels of 22 RNA biomarkers involved in multiple biological pathways that are associated with the development and progression of aggressive prostate cancer. The test has been validated for use on FFPE samples of tissue removed during surgery in patients with adverse pathology or other high risk factors. The expression data is used to calculate the probability of clinical metastasis within five years of radical prostatectomy surgery, classifying patients into genomic risk categories for metastasis to aid in treatment recommendations post-surgery . The Decipher test is intended to provide physicians with additional information to aid in treatment and management decisions.
The Decipher test is also marketed for use on FFPE samples of biopsy tissue, where it may be used as a potential risk assessment and management tool to help determine whether a patient with localized cancer is a good candidate for active surveillance post-biopsy. The test is accepted for use in patients who present with a very low, low, favorable, and unfavorable intermediate risk biopsy result according to NCCN Guidelines upon pathologic evaluation.

Oncotype DX® Prostate Cancer Assay

The Oncotype DX Prostate Cancer Assay is a genetic test that uses quantitative RT-PCR methodology to measure the expression levels of 17 genes in a sample of the tumor tissue at the time of biopsy. Twelve of the genes assayed are thought to be associated with adverse tumor pathology, biochemical recurrence, metastasis, or prostate cancer death.[10] Using a proprietary algorithm, gene expression levels are used to calculate a Genomic Prostate Score (GPS) that indicates a tumor's potential aggressiveness.[10]

Oncotype DX prostate cancer test is intended to predict the likelihood of aggressive prostate cancer in patients who have received a diagnosis of very low, low, or low-intermediate-risk prostate cancer, based on NCCN criteria.[10] If the test results in a low GPS score, then taken together with other

clinicopathologic factors (e.g., Gleason score and PSA level), the patient may be managed using active surveillance instead of undergoing radical prostatectomy and/or radiation treatment.[10]

Oncotype DX® AR-V7 Nucleus Detect Test

The Oncotype DX® AR-V7 Nucleus Detect test is a liquid biopsy test that analyzes circulating tumor cells in the patient's blood to detect nuclear expression of AR-V7, a variant of the androgen receptor that is resistant to androgen-receptor signaling inhibitor (ARSI) therapy. The test is intended to guide treatment with ARSI therapy or with chemotherapy in patients with metastatic castration-resistant prostate cancer (mCRPC).[11]

Prolaris® (Myriad Genetics, Inc.)

The Prolaris Genetic Test is a RT-PCR test conducted on FFPE tissue samples collected during standard prostate biopsy or radical prostatectomy, or on tissue from prepared slides. The test measures RNA expression levels of 46 genes, 31 of which are cell-cycle genes in the fraction of tumor cells that are actively dividing, thus providing an indirect measure of cancer growth rate. Assay results are reported as a CCP score, also called the Prolaris Score, which denotes the risk of progression.[5]

The Prolaris Genetic Test is intended to be used in addition to other clinicopathologic factors to assist clinicians in predicting disease aggressiveness within a 10-year window for patients with an initial diagnosis of prostate cancer to inform treatment decisions. The test is also intended to help estimate the risk of biochemical recurrence in post-prostatectomy patients to adjust monitoring intervals or treatment strategies. Patients identified as being high risk, by way of a high CCP score, may be candidates for active treatment. Prolaris scores are intended to provide additional information for clinical decision making.[5]

Patients receiving adjuvant hormonal therapy and radiation treatment before biopsy are not candidates for Prolaris testing because treatment effects can interfere with interpretation of test results. Prolaris has also not been validated for patients with PSA levels over 100 ng/mL (nanograms per milliliter).[5]

ProMark (Metamark Genetics Inc.)

The ProMark Proteomic Prognostic test quantitatively measures levels of eight protein biomarkers in FFPE prostate biopsy tissue samples using multiplex immunofluorescent staining with monoclonal antibodies. A proprietary algorithm captures digitalized quantitative measurements that are used to generate the ProMark Risk Score. The ProMark Risk Score is used to determine a personalized risk of prostate cancer aggressiveness.[12]

REGULATORY STATUS

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Approval or clearance by the Food and Drug Administration (FDA) does not in itself establish medical necessity or serve as a basis for coverage. Therefore, this section is provided for informational purposes only.

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

The analytical and clinical validity of these assays have been established; therefore, the evidence review below will focus on the clinical utility of these tests to determine whether testing improves treatment management or overall patient-relevant health outcomes.

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the clinical utility of protein biomarker and genetic tests as tools for screening, detection, diagnosis, prognosis or management of prostate cancer. Below is a summary of the available evidence identified through February 2026.

Molecular Assays Used for Prostate Cancer Detection

4Kscore Test

Systematic Reviews

- In 2022, Hayes conducted a genetic test evaluation report assessing the 4Kscore Test's utility in prostate cancer biopsy decision making.[13] Having systematically searched the literature, investigators identified 1 study evaluating the test's analytical validity, 3 studies evaluating clinical validity and 1 study evaluating clinical utility. Sample sizes ranged from 162 to 1012. Findings from the 1 analytical validity study reported that a digital rectal examination conducted before the 4kscore blood draw could affect results. Authors from the 3 assessed clinical validity studies concluded that evidence from the 4Kscore Test could estimate a patient's percentage of risk for aggressive prostate cancer if a prostate biopsy were performed. No studies reported evidence that the Test provided information on the 10-year likelihood of developing distant metastases when the Test result is <7.5%. The one clinical utility study concluded that the Test could influence subsequent decision to proceed with biopsy; however, the study evaluated no patient outcomes. Evidence quality across all studies was rated as ranging from "very-poor" to "poor." Hayes ultimately assigned a "D2" rating (insufficient evidence) for use of the 4kscore Test to aid in prostate cancer biopsy decision making for physician and patient via estimating patients' percentage of risk for aggressive prostate cancer if a biopsy were performed and, secondly, providing information on the 10-year likelihood of developing distant metastases when the 4k score result is <7.5%.

- In 2018, ECRI conducted a systematic review evaluating the utility of the 4Kscore Test in assessing the risk of aggressive prostate cancer before initial or repeat biopsy.[14] Having evaluated the same studies assessed in the Hayes review discussed above, ECRI investigators concluded that evidence was "inconclusive" regarding the clinical utility of 4Kscore testing. Evaluated studies reported changes in patient management following test results, but not health outcomes. Moreover, evidence assessing clinical validity was mixed as to whether adding 4kscore to clinical risk factors was more accurate than clinical risk factor models alone. ECRI identified no ongoing clinical trials that would address these evidence gaps.

Nonrandomized Studies

- In 2015, Konety et al. published the results of an uncontrolled retrospective case series (n=611 patients) that suggested that 4Kscore Test results influenced biopsy decisions in 89% of tested patients and reduced the number of prostate biopsies by 65%.[15] The actual percentage of cases not proceeding to biopsy were 94.0%, 52.9%, and 19.0% for men who had low-, intermediate-, and high-risk 4kScore test results, respectively, indicating that a substantial proportion of men considered to be at high-risk opted to not proceed to biopsy. However, this study did not report any follow up of patients and therefore no long-term data was reported on patient outcomes such as morbidity or mortality as a result of 4Kscore testing. Of note, in the short term, foregoing an unnecessary prostate biopsy may reduce biopsy-related complications in patients who have low-risk or no prostate cancer. However, in men deemed to be of high risk, foregoing biopsy as a result of 4Kscore testing may delay diagnosis, which could result in could result in increased morbidity and/or mortality in this patient population. Therefore, studies reporting long-term patient outcomes after use of the 4Kscore test are needed.

ConfirmMDx

Systematic Reviews

- In 2019, reviewed in 2022, Hayes conducted a genetic test evaluation report evaluating the utility of ConfirmMDx in prostate cancer biopsy decision making.[16] Having systematically searched the literature, investigators identified 1 study evaluating analytical validity, 4 studies evaluating clinical validity, and 1 study evaluating clinical utility. Sample sizes ranged from 138 to 803 men. Median follow-up was approximately 9 months. Findings from the 1 analytical validity study reported that the multiplex assay is accurate and reproducible on biopsy samples for both determining methylation positive versus negative and the methylation intensity. Clinical validity studies showed that ConfirmMDx results are negative in patients with a repeat negative prostate biopsy. One small preliminary study assessing clinical utility reported that most men with a negative ConfirmMDx result will not have repeat biopsy within 9 months of a negative prostate biopsy. The rate of repeat biopsies was not compared with the repeat biopsy rate in men receiving standard care, thus limiting generalizations regarding clinical utility. No study reported clinical outcomes in men with both positive and negative ConfirmMDx results.

  Overall evidence quality was assessed as "very low." Limitations included all tests' manufacturer funding and a lack of large studies evaluating diverse populations of men that compared the clinical accuracy of detecting high-grade prostate cancer with ConfirmMDx. Hayes ultimately assigned a "D2" rating (insufficient evidence) for use of the ConfirmMDx test using residual prostate biopsy specimens, to "rule out men who are prostate cancer free; and [secondly] identify men at risk for undetected prostate cancer by predicting the likelihood of detecting Gleason score ≤ 6 and ≥ 7 prostate cancer on repeat biopsy in men with an initial negative biopsy yet high-risk clinicopathological features suggestive of prostate cancer."[16]

- In 2022, ECRI conducted a systematic review evaluating the utility of the ConfirmMDx Test for determining need for repeat prostate biopsy.[17] Having evaluated 3 of the retrospective cohort studies assessed in the Hayes review discussed above, ECRI investigators concluded that evidence was "inconclusive" regarding the clinical utility of the ConfirmMDx Test. Evaluated

studies reported that the repeat biopsy rate in patients managed with ConfirmMDx, but neither directly compared that rate to patients managed without ConfirmMDx nor reported on patient health outcomes. While data from the 2 clinical validity studies showed ConfirmMDx can help identify patients at low risk of prostate cancer; approximately 10% of patients with negative ConfirmMDx results have positive biopsy results. Investigators called for additional prospective and comparative studies to establish ConfirmMDX's clinical validity and clinical utility.

Nonrandomized Studies

- In 2014, Wojno et al. published a preliminary retrospective case series that attempted to evaluate the effect of utilization of ConfirmMDx on reducing the rate of repeat prostate biopsies in men with a negative biopsy by histopathologic analysis. While only six of 138 (4.3%) patients proceeded to a repeat biopsy based on a negative assay result, the authors stated that, "the results are only indicative of the potential that the epigenetic assay may have on patient management." Although the aim of the study was to demonstrate a low repeat biopsy rate based on the results of the ConfirmMDx test; the biopsy rate of those who underwent testing was not compared to the repeat biopsy rate of men receiving standard care. In addition, the short-term follow-up of this study (median of nine months) was not long enough to evaluate true repeat biopsy rates, since men undergoing active surveillance would likely go back for re-evaluation every 6-12 months, based on NCCN's current recommendations. Therefore, this single clinical utility study does not provide conclusive evidence of reduction of biopsy procedures solely due to ConfirmMDx. Furthermore, no prospective studies have been published to show that use of ConfirmMDx reduces the number of repeat biopsies across diverse clinical settings with potentially varied disease prevalence.

<u>Progensa® PCA3 Assay</u>

- In 2021, ECRI conducted a systematic review and concluded that evidence was insufficient to support the use of the PCA3 assay due to conflicting results among the six identified published clinical validity studies.[4] The review stated "ascertaining whether Progensa can be used to aid in determining the need for repeat prostate biopsy is not possible from the available evidence" and noted that the cut-off scores used in the studies all differed and that there was some evidence that the test resulted in false negatives in some cases. The review did not identify any studies reporting on clinical utility.

- In 2014 (updated 2015; archived 2018), Hayes published a review that evaluated the PCA3 for its ability to detect prostate cancer, including nine uncontrolled case series (n=127-926 patients) that evaluated the clinical utility of PCA3 testing in improving risk assessment and facilitating decisions regarding prostate biopsy in men with one or more risk factors.[18] Although several of these studies reported that when PCA3 was incorporated into multi-variable biopsy models (also known as nomograms) there was improved diagnostic accuracy, the variables included in the nomograms differed between studies and only one of the studies was comparative. These modelling studies suggest that the PCA3 score could be incorporated into an algorithm for improved biopsy outcome, but actual management decisions regarding biopsy and how those decisions affected health outcomes were not reported. The review did not identify any studies that prospectively evaluated changes in patient outcomes or treatment decisions based on incorporation of PCA3 score. Consequently, although there is potential for clinical utility, the

review concluded that studies were needed that directly demonstrate the impact of this test on the care of patients being evaluated for prostate cancer. Due to insufficient evidence of direct clinical utility, the review assigned the PCA3 assay a grade of "C" for prostate cancer screening in men considering prostate biopsy.

Nonrandomized Studies

In addition to the Hayes review above, Ruffion et al. published two case series suggesting that the use of PCA3 in two different nomograms led to potential reductions in unnecessary biopsies of 48-52% with increases in missed prostate cancers of 6-15% using either a *PCA3*-based nomogram or *PCA3* level corrected for prostate volume (*PCA3* density). However, neither series assessed utility of the test for actual clinical decision-making, since all patients underwent biopsy regardless of results from the nomogram. In addition, neither study evaluated patient specific outcomes such as recurrence or survival.

Prostate Health Index (PHI) (Beckman Coulter Inc.)

- In 2023, Hayes published a Molecular Test Assessment on the Prostate Health Index (PHI) for prebiopsy triage (Beckman Coulter).[2] Hayes included 2 studies for analytical validity, 5 studies for clinical validity, and 2 studies for clinical utility, by Tosoian et al, is summarized below. Hayes gave the PHI test for prebiopsy triage in men ≥ 50 years of age a Hayes rating of C, based on low-quality evidence for clinical validity and very-low-quality evidence for analytical validity and clinical utility, stating that there is insufficient evidence to assess the impact on health outcomes.

- In 2017, Tosoian et al. published the results of a case-control study that evaluated the effect of the PHI on incidence of initial biopsy, including 345 cases and 231 controls.[19] The incidence of biopsy was significantly lower ($p<0.001$) in men who had PHI testing (39%) compared with those that did not (48%), suggesting that the PHI may impact prostate biopsy decisions. However, this study did not evaluate the role the PHI had in biopsy decision, nor were the impact on prostate cancer diagnosis or subsequent health outcomes assessed.

SelectMDx

- In 2024, Hayes published a molecular test assessment for the SelectMDx test (MDxHealth Inc) for prostate cancer.[20] The review included 1 study on analytical validity, 3 studies on clinical validity, and one study on clinical utility. The one study on clinical utility by Shore and colleagues was a retrospective review evaluating the impact of the SelectMDx test on patient management practice. The biopsy rate in SelectMDx test positive men were 60% (99/163) compared to 12% (32/255) for SelectMDx test negative men ($P<0.001$); however, as this was a retrospective chart review, the authors could not confirm to what, if any, extent the test impacted biopsy decision. Furthermore, the impact on patient outcomes is also unclear. Overall, there is very-low-quality evidence to support the clinical utility of the SelectMDx test. The reviewers gave SelectMDx a Hayes rating of D2, stating that there was insufficient evidence supporting use of the test and additional studies are needed to demonstrate clinical validity and clinical utility.

- In 2020, ECRI published a genetic test assessment of SelectMDx (MDxHealth Liquid Biopsy Test for assessing risk of aggressive prostate cancer. ECRI identified 2 single-arm studies reporting on clinical utility that found that 44% of patients who received a negative test result "may safely skip prostate biopsy," while 4 to 12% of patients who received negative SelectMDx tests may "be at risk of diagnostic delay if they forgo a biopsy." ECRI concluded that these studies had a high risk of bias and therefore no conclusions could be made on the clinical utility of the test. They gave SelectMDx an evidence bar rating of "Evidence is inconclusive: too few clinical utility data".[9]

ExoDx Prostate (also known as IntelliScore)

- In 2023, Hayes completed a molecular test assessment on ExoDx Prostate Test.[21] A total of 4 unique studies were included in the assessment, with all four reporting clinical validity outcomes, and one also reporting outcomes related to clinical utility. Patient sample size ranged from 190-519 patients. The assessment concluded that there was a very low-quality body of evidence that was insufficient to assess the clinical benefit of the ExoDx Prostate test. Hayes gave the test a D2 rating, insufficient evidence. The assessment stated that the low quality evidence and small amount of literature played into the evidence rating.

- ECRI published a genetic test assessment on ExoDx Prostate in 2023.[22] Evidence was reviewed from one systematic review, one randomized controlled trial, one pooled cohort analysis, one cohort study, and one diagnostic cohort study. Studies suggest that ExoDx results may allow 10-30% of patients to safely forgo biopsy; however, ExoDx may miss up to 5% of aggressive tumors. The authors found the data was too limited in quantity and quality to enable a firm conclusion about how ExoDx's clinical validity and utility compare with those of other diagnostic screening tools for aggressive prostate cancer. ECRI listed an evidence bar of "potential benefits but very-low-quality data". ECRI noted that additional large, multicenter RCTs that compare ExoDx's accuracy directly with that of other urine biomarkers as well as MRI that report on clinical validity are needed.

Other Assays

Clinical utility studies using assay results for decision-making for initial biopsy or repeat biopsy were not identified for any other molecular assay proposed as a tool to detect prostate cancer, including but not limited EpiScore, NeoLAB Prostate Liquid Biopsy, PanGIA Prostate, and Mi-Prostate Score. In addition, no studies were identified that reported on health outcomes such as recurrence or survival of patients that underwent testing using any of the assays described above.

Molecular Assays used for Prognosis or Treatment

Decipher

In 2024, Hayes published a review on the Decipher prostate cancer classifier test, including three industry-sponsored clinical utility studies that reported on decision impact of the Decipher test.[23-26] The review noted that the Decipher test was reported by some studies, "to have greater ability than clinicopathologic features alone to predict metastasis in high-risk men, and there was some indication that it could improve predictive performance of clinicopathologic models." However, measures of test

performance were not consistent across studies, and it was unclear whether Decipher added enough prognostic information compared to current clinicopathologic models to change patient management decisions and improve outcomes. In addition, the included studies consisted of relatively small case series (ranging from 121 to 266 patients) and all four studies suffered from similar limitations including that the actual treatment administered was not tracked, patient outcomes were not assessed, and the urologists who participated in the studies were likely not representative of all urologists. As a result, Hayes rated the use of the Decipher test with a "D2" rating, indicating that additional independent studies reporting actual clinical utility measures are needed.

Oncotype DX® Prostate Cancer Test

- In 2020, ECRI conducted a systematic review evaluating the utility of the Oncotype DX Genomic Prostate Score (GPS) Test in assessing prostate cancer prognosis.[10] Having evaluated 3 clinical validity studies assessed in the Hayes review discussed below, including 3 clinical utility studies, ECRI investigators concluded that evidence was "inconclusive" regarding the clinical utility of the Oncotype DX Genomic Prostate Score. Evaluated studies reported that results may affect patient management decisions; however, no data reported the impact that those changes had on patient health outcomes. While some clinical validity evidence suggested that GPS correlates with incidence of adverse pathology, no studies reported 10-year prostate cancer-specific mortality or metastasis rates.

- In 2018, reviewed in 2023, Hayes published a review on the Oncotype DX Genomic Prostate Score (GPS) Assay.[27] One case series of 158 men reported an 18% absolute change in treatment recommendation between active surveillance and immediate treatment after assay results and a 26% change in treatment choice/intensity after assay results.[28] In contrast, a second retrospective chart review of 211 patients reported no significant difference in the recommendation of active surveillance/watchful waiting between baseline patients and those with Oncotype assay scores.[29] However, there was a significant difference in active surveillance/watchful waiting as the single treatment received between baseline patients and patients with a GPS. Although the results from the two clinical utility studies suggest that Oncotype DX could potentially affect initial treatment decisions in patients whose very low or low risk status is modified based on assay results, no study has been identified to determine whether Oncotype DX score results improve long-term health outcomes, such as overall survival. As a result, Hayes rated the use of the Oncotype DX prostate cancer test with a "D2" grade due to very low utility evidence of clinical utility, stating that long-term clinical utility studies are needed.

Oncotype DX® AR-V7 Nucleus Detect Test

Systematic Reviews

- In 2024, Hayes conducted an evidence review evaluating the validity and utility of the Oncotype DX AR-V7 Nucleus Detect Test.[30] In total, 1 analytical validity study and 3 clinical validity studies were included for review. No peer-reviewed studies were identified that addressed the clinical utility of the Oncotype DX AR-V7 Nucleus Detect test. Investigators concluded that there is a very low quality body of evidence indicating the test will identify metastatic castration-resistant prostate cancer patients who are not likely to respond to AR-targeted therapies. Additional

studies with larger cohorts of patients were judged necessary to demonstrate that the test could support physician clinical decision-making and improve patient health outcomes.

- In 2019, ECRI conducted a systematic review evaluating the utility of the Oncotype DX AR-V7 Nucleus Detect Test for informing treatment of metastatic castration-resistant prostate cancer.[11] Having systematically searched the literature through October 2018, investigators reviewed 2 prospective studies (n=303), neither of which assessed the test's clinical validity or utility. While data from one cross-sectional correlation study provided indirect evidence of test utility, results from other studies to date have been mixed. ECRI investigators concluded that evidence was "inconclusive" regarding the clinical utility of the Oncotype DX AR-V7 Nucleus Detect Test. To assess clinical validity and utility, authors called for large, diagnostic and longitudinal cohort studies assessing outcomes after patients undergo therapy guided by AR-V7 test results.

Nonrandomized Controlled Trials

- In 2019, Sharp and colleagues evaluated the reproducibility of AR-V7 testing, and associations with clinical characteristics, circulating tumor cell counts, tumor biopsy AR-V7 protein expression and overall survival.[31] Researchers determined AR-V7 status via blood samples from patients with mCRPC (n=181), circulating tumor cell counts (n=136) and matched biopsies (n=58). In total, 95/277 samples tested positive for circulating tumor cells and negative for AR-V7, while 96/277 samples were positive for both circulating tumor cells and AR-V7. When controlling for baseline characteristics, overall survival was shorter in patients with positive circulating tumor cells and positive AR-V7 than in participants with negative circulating tumor cells. No evidence was found that patients with positive circulating tumor cells and positive AR-V7 had worse overall survival than participants with positive circulating tumor cells and negative AR-V7 (HR 1.26; 95% CI 0.73-2.17; p = 0.4). Limitations included the heterogeneity of treatments, which prevented investigators form evaluating AR-V7 expression as a predictive biomarker of response to treatment. Authors concluded that "robust clinical qualification of these [AR-V7] assays is required before their routine use."

- In 2019, Armstrong and colleagues conducted a prospective, blinded validation study of two circulating tumor cell AR-V7 assays in predicting progression-free survival and overall survival with abiraterone or enzalutamide in patients with mCRPC.[32] Among 118 patients with high-risk mCRPC, 55 patients were treated with abiraterone, 58 were treated with enzalutamide, and 5 received both therapies concurrently. Median follow-up time among surviving participants was 19.6 months. Among all patients, median progression-free survival was 5.8 months (95% CI, 4.1 to 7.6 months) and median overall survival (OS) was 20.3 months (95% CI, 17.0 to 27.2 months). AR-V7 detection by both the Johns Hopkins and Epic AR-V7 assays was independently associated with shorter PFS (HR: 1.9 [95% CI, 1.1 to 3.3; P = .032] and 2.4 [95% CI, 1.1 to 5.1; P = .020], respectively) and OS (HR: 4.2 [95% CI, 2.1 to 8.5] and 3.5 [95% CI, 1.6 to 8.1], respectively) after adjusting for CTC number and clinical prognostic factors. Men with AR-V7–positive mCRPC had fewer confirmed prostate-specific antigen responses (0% to 11%) or soft tissue responses (0% to 6%). The observed percentage agreement between the two AR-V7 assays was 82%. Only 11 and 28 participants who tested positive for AR-V7 by the two different assays. Investigators concluded that larger controlled studies were needed to confirm the predictive value of AR-V7.

Prolaris®

Systematic Reviews

In 2022, Hayes published a systematic review assessing the clinical utility of the Prolaris Biopsy Test for determination of the 10-year risk of metastatic disease after definitive therapy and disease-specific mortality if conservatively managed.[33] Investigators systematically searched the literature through March 2019. In total, 10 studies were examined in detail, assessing analytical validity (n=2), clinical validity (n=6), and clinical utility (n=2). Sample sizes ranged from 123 to 19,215; follow-up ranged from 3 months to 11.8 years. Results from 1 analytical validity study suggested that the cell cycle progression (CCP) score was reproducible, while another study showed that DNA contamination may affect CCP scores. Six clinical validity studies reported preliminary evidence that CCP score and cell cycle risk (CCR) score may aid in predicting prostate cancer-specific mortality and metastasis. While two clinical utility studies suggested that the Prolaris Biopsy test may influence treatment decisions, no studies to date have provided direct evidence that the test drives decision making or reported subsequent clinical outcomes. Overall evidence quality was assessed as "very low." Investigators ultimately assigned a "D2" rating (insufficient evidence) and concluded that evidence was insufficient to support the use of the Prolaris test. Authors called for additional tests demonstrating the Prolaris test's accuracy, reproducibility and clinical utility.

Nonrandomized Controlled Trials

Two large prospective case series (n=305 and 1206 patients) and one small case-control study have been published that evaluated whether the use of the Prolaris test changed patient management.[34-36] Both series performed Prolaris testing on initial prostate biopsy tissue and reported that between 37.2- 72.1% patients had a reduction in treatment and 23.4-26.9% had an increase in treatment based on test results. Only one of the studies, which was industry-sponsored, tracked patients after treatment recommendation were made to ensure adherence (median three months follow-up post-test).[34] While the results of these two studies suggest that Prolaris testing results can be used to personalize treatment decisions, they did not report on patient outcomes.

In addition, studies assessing the effect of Prolaris on patient patient-important outcomes, such as biochemical recurrence, cancer-specific survival or long-term survival, are lacking. Therefore, prospective studies are needed that compare health outcomes between patients managed based on Prolaris test results and those managed with standard clinical risk predictors. This conclusion was also reached by a 2017 ECRI review, that reported that the evidence for the use of the Prolaris test was inconclusive because none of the available studies (seven clinical validity and two clinical utility studies) directly showed that Prolaris use improved patient health outcomes. The review concluded that "limited evidence shows that Prolaris works as intended for predicting disease aggressiveness and identifying patients at higher risk for recurrence."[5]

ProMark

In 2016 (archived in 2021), Hayes published a genetic test evaluation report evaluating the ProMark Proteomic Prognostic Test.[12] In total, 3 analytical validity studies and 2 clinical validity studies were included for review. Sample sizes ranged from 380 to 508 for analytical validity studies and 276 to 282 for clinical validity studies. Despite preliminary evidence of clinical validity for the test prognostic value,

neither study measured the test's repeatability, reproducibility, limits of detection, and analytical sensitivity and specificity. Evidence was insufficient to determine the benefits of using ProMark for risk stratification over the use of standard clinicopathological methods. No clinical utility studies have been published to date providing evidence for the ProMark test. Overall evidence quality was assessed as "very-low." Hayes ultimately assigned a "D2" rating (insufficient evidence) for the use of the ProMark Proteomic Prognostic Test to provide a personalized prediction of prostate cancer aggressiveness in patients with biopsy Gleason scores of 3+3 and 3+4.

CLINICAL PRACTICE GUIDELINES

National Institutes of Health and Care Excellence (NICE)

In 2021, NICE published a clinical practice guideline addressing the diagnosis and management of prostate cancer.[37] Citing a lack of clinical evidence, investigators recommended against the use of the Progensa PCA3 assay and the Prostate Health Index in patients undergoing evaluation for suspected prostate cancer who have had a negative or inconclusive prostate biopsy.

American Urological Association (AUA)/American Society for Radiation Oncology (ASTRO)/Society of Urologic Oncology (SUO)

In 2022, investigators representing the AUA/ASTRO/SUO published an evidence-based clinical practice guideline addressing clinically localized prostate cancer.[38] The guideline statements include:
"Risk assessment:

- Clinicians may selectively use tissue-based genomic biomarkers when added risk stratification may alter clinical decision-making. (Expert Opinion)
- Clinicians should not routinely use tissue-based genomic biomarkers for risk stratification or clinical decision-making. (Moderate Recommendation; Evidence Level: Grade B)"

National Comprehensive Cancer Network (NCCN)

In 2026, the NCCN published updated guidelines (Version 5.2026) for the diagnosis and treatment of prostate cancer.[39] Despite noting a lack of demonstrated clinical utility, investigators stated that (Decipher, Oncotype DX Prostate, and Prolaris) are optional adjuncts that may be considered to assist with risk stratification in patients with NCCN low-, favorable intermediate-, unfavorable intermediate-, or high-risk localized prostate cancer and a life expectancy of ≥10 years.

<u>Protein Biomarker Testing</u>

In 2026, NCCN published updated guidelines (Version 2.2026) for Prostate Cancer Early Detection.[40] The guidelines recommend the following:

- "Biomarkers that improve specificity of detection are not, as yet, mandated as first-line screening tests in conjunction with serum PSA. However, there may be some patients who meet PSA standards for consideration of prostate biopsy, but for whom the patient and/or the physician wish to more precisely estimate risk.

- *Prior to initial biopsy*: Tools that meet most or all of the above criteria based on available data include the Prostate Health Index (PHI), SelectMDx, 4Kscore, ExoDx Prostate Test, MyProstateScore (MPS), MPS 2.0 (MPS2), Stockholm3, and IsoPSA.
- *After initial negative biopsy*: Tests that meet most or all of the above criteria based on available data include percent-free PSA, 4Kscore, PHI, ConfirmMDx, ExoDX Prostate Test, MPS, MPS2 , and IsoPSA."

American Society of Clinical Oncology (ASCO)

In 2020, ASCO published guidelines on molecular biomarkers in localized prostate cancer. The guidelines recommend the following:[41]

- "Are there molecular biomarkers to identify patients with prostate cancer who are most likely to benefit from active surveillance? 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 have an impact on patient management. Routine ordering of molecular biomarkers is not recommended (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).
- Are there molecular biomarkers to diagnose clinically significant 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 have an impact on patient management. Routine ordering of molecular biomarkers is not recommended (Type: evidence-based; Evidence quality: intermediate; Recommendation: moderate).
- Are there molecular biomarkers to guide the decision between postprostatectomy adjuvant versus salvage radiation? The Expert Panel recommends consideration of a commercially available molecular biomarker (eg, Decipher Genomic Classifier) in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to have an impact on patient management. In the absence of prospective clinical trial data, routine use of genomic biomarkers in the postprostatectomy setting to determine adjuvant versus salvage radiation or to initiate systemic therapies should not be offered (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate)."

ASCO notes that there is no high-level evidence showing that molecular biomarker testing for management decisions improves quality of life or cancer-specific outcomes and recommends continued investigation of these tests through clinical trials.

EVIDENCE SUMMARY

Consistent, lower-quality evidence suggests that certain protein biomarker tests may aid in the management of prostate cancer post-biopsy. Certain assays show promise when used in conjunction with commonly evaluated clinical pathologic factors such as digital rectal exam (DRE) and prostate specific antigen (PSA) tests. While additional evidence is needed to demonstrate clinical utility, current clinical practice guidelines, including those published by the National Comprehensive Cancer Network (NCCN), recommend the use of select protein biomarker test for select patients in specific clinical situations.

HEALTH EQUITY CONSIDERATIONS

The Centers for Disease Control and Prevention (CDC) defines health equity as the state in which everyone has a fair and just opportunity to attain their highest level of health. Achieving health equity requires addressing health disparities and social determinants of health. A health disparity is the occurrence of diseases at greater levels among certain population groups more than among others. Health disparities are linked to social determinants of health which are non-medical factors that influence health outcomes such as the conditions in which people are born, grow, work, live, age, and the wider set of forces and systems shaping the conditions of daily life. Social determinants of health include unequal access to health care, lack of education, poverty, stigma, and racism.

The U.S. Department of Health and Human Services Office of Minority Health calls out unique areas where health disparities are noted based on race and ethnicity. Providence Health Plan (PHP) regularly reviews these areas of opportunity to see if any changes can be made to our medical or pharmacy policies to support our members obtaining their highest level of health. Upon review, PHP creates a Coverage Recommendation (CORE) form detailing which groups are impacted by the disparity, the research surrounding the disparity, and recommendations from professional organizations. PHP Health Equity COREs are updated regularly and can be found online here.

BILLING GUIDELINES AND CODING

CODES*		
CPT	0005U	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score
	0011M	Oncology, prostate cancer, mRNA expression assay of 12 genes (10 content and 2 housekeeping), RT-PCR test utilizing blood plasma and/or urine, algorithms to predict high-grade prostate cancer risk
	0021U	Oncology (prostate), detection of 8 autoantibodies (ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2),
	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
	0113U	Oncology (prostate), measurement of PCA3 and TMPRSS2-ERG in urine and PSA in serum following prostatic massage, by RNA amplification and fluorescence-based detection, algorithm reported as risk score
	0133U	Hereditary prostate cancer–related disorders, targeted mRNA sequence analysis panel (11 genes) (List separately in addition to code for primary procedure)
	0228U	Oncology (prostate), multianalyte molecular profile by photometric detection of macromolecules adsorbed on nanosponge array slides with machine learning, utilizing first morning voided urine, algorithm reported as likelihood of prostate cancer
	0339U	Oncology (prostate), mRNA expression profiling of HOXC6 and DLX1, reverse transcription polymerase chain reaction (RT-PCR), first-void urine following

		digital rectal examination, algorithm reported as probability of high-grade cancer
	0343U	Oncology (prostate), exosome-based analysis of 442 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as molecular evidence of no-, low-, intermediate- or high-risk of prostate cancer
	0359U	Oncology (prostate cancer), analysis of all prostate-specific antigen (PSA) structural isoforms by phase separation and immunoassay, plasma, algorithm reports risk of cancer
	0403U	Oncology (prostate), mRNA, gene expression profiling of 18 genes, first-catch urine, algorithm reported as percentage of likelihood of detecting clinically significant prostate cancer
	0424U	Oncology (prostate), exosome-based analysis of 53 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RTqPCR), urine, reported as no molecular evidence, low-, moderate- or elevated-risk of prostate cancer
	0433U	Oncology (prostate), 5 DNA regulatory markers by quantitative PCR, whole blood, algorithm, including prostate-specific antigen, reported as likelihood of cancer
	0475U	Hereditary prostate cancer-related disorders, genomic sequence analysis panel using next-generation sequencing (NGS), Sanger sequencing, multiplex ligation-dependent probe amplification (MLPA), and array comparative genomic hybridization (CGH), evaluation of 23 genes and duplications/deletions when indicated, pathologic mutations reported with a genetic risk score for prostate cancer
	0495U	Oncology (prostate), analysis of circulating plasma proteins (tPSA, fPSA, KLK2, PSP94, and GDF15), germline polygenic risk score (60 variants), clinical information (age, family history of prostate cancer, prior negative prostate biopsy), algorithm reported as risk of likelihood of detecting clinically significant prostate cancer
	0497U	Oncology (prostate), mRNA gene-expression profiling by real-time RT-PCR of 6 genes (FOXM1, MCM3, MTUS1, TTC21B, ALAS1, and PPP2CA), utilizing formalinfixed paraffin-embedded (FFPE) tissue, algorithm reported as a risk score for prostate cancer
	0534U	Oncology (prostate), microRNA, single-nucleotide polymorphisms (SNPs) analysis by RT-PCR of 32 variants, using buccal swab algorithm reported as a risk score
	~~0550U~~	**TERMED 1/1/2026** ~~Oncology (prostate), enzyme-linked immunosorbent assays (ELISA) for total prostate-specific antigen (PSA) and free PSA, serum, combined with age, previous negative prostate biopsy status, digital rectal examination findings, prostate volume, and image and data reporting of the prostate, algorithm reported as a risk score for the presence of high-grade prostate cancer~~
	0572U	Oncology (prostate), high-throughput telomere length quantification by FISH, whole blood, diagnostic algorithm reported as risk of prostate cancer
	0591U	Oncology (prostate cancer), biochemical analysis of 3 proteins (total PSA, free PSA, and HE4), plasma, serum, prognostic algorithm incorporating 3 proteins

		and digital rectal examination, results reported as a probability score for clinically significant prostate cancer
	0609U	Oncology (prostate), immunoassay for total prostate-specific antigen (PSA) and free PSA, serum or plasma, combined with clinical features, algorithm reported as a probability score for clinically significant prostate cancer
	81313	PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)
	81479	Unlisted molecular pathology procedure
	81539	Oncology (high-grade prostate cancer), biochemical assay of four proteins (Total PSA, Free PSA, Intact PSA, and human kallikrein-2 [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 score
	81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis 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
	81599	Unlisted multianalyte assay with algorithmic analysis
	84999	Unlisted chemistry code

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

REFERENCES

1. American Cancer Society. Prostate Cancer. https://www.cancer.org/cancer/prostate-cancer/about/what-is-prostate-cancer.html. Published 2023. Accessed 3/21/2025.
2. Hayes Inc. The Prostate Health Index for Prebiopsy Triage (Beckman Coulter Inc.). December 9, 2022. https://evidence.hayesinc.com/report/gte.prostateindex4105. Published 2023. Accessed 3/20/2026.

3. National Comprehensive Cancer Network (NCCN). Prostate Cancer Early Detection (Version 1.2025). https://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf. Published 2024. Accessed 3/20/2025.
4. ECRI. Progensa PCA3 Assay (Hologic, Inc.) for Determining the Need for Repeat Prostate Biopsy. https://members.ecri.org/search?k=Progensa+PCA3+Assay&page=1&pageSize=20&sort=relevance&dr=false. Published 2021. Accessed 3/20/2026.
5. ECRI. Prolaris Genetic Test (Myriad Genetics, Inc.) for Determining Prostate Cancer Prognosis. June 2021. https://members.ecri.org/search?k=Prolaris+&page=1&pageSize=20&sort=relevance&dr=false. Published 2021. Accessed 3/20/2026.
6. MDxHealth Website. ConfirmMDx. https://mdxhealth.com/confirmmdx-physician/. Accessed 3/15/2022.
7. Van Neste L, Groskopf J, Grizzle WE, et al. Epigenetic risk score improves prostate cancer risk assessment. *Prostate.* 2017;77(12):1259-1264.
8. NeoGenomics test menu. NeoLAB Prostate Liquid Biopsy. Updated 2017. https://neogenomics.com/test-menu/neolab-prostate. Accessed 1/30/2021.
9. ECRI. SelectMDx (MDxHealth) Liquid Biopsy Test for Predicting Risk of Aggressive Prostate Cancer. https://members.ecri.org/search?k=SelectMDx&page=1&pageSize=20&sort=newest&dr=false. Published 2020. Accessed 3/20/2026.
10. ECRI. Oncotype DX Prostate Cancer Assay (Genomic Health, Inc.) for Predicting Aggressiveness of Prostate Cancer. http://members.ecri.org/search?k=Oncotype+DX+prostate&page=1&pageSize=20&sort=relevance&dr=false. Published 2020. Accessed 3/20/2026.
11. ECRI. Oncotype DX AR-V7 Nucleus Detect Test (Genomic Health, Inc., and Epic Sciences, Inc.) for Informing Treatment of Metastatic Castration-resistant Prostate Cancer. https://members.ecri.org/search?k=Oncotype+DX+AR-V7&page=1&pageSize=20&sort=relevance&dr=false. Published 2019. Accessed 3/20/2026.
12. Hayes Inc. ProMark Proteomic Prognostic Test (Metamark Genetics Inc.). https://evidence.hayesinc.com/report/gte.promark3837. Published 2021 (Archived). Accessed 3/20/2026.
13. Hayes Inc. 4Kscore Test (OPKO Health Inc.). https://evidence.hayesinc.com/report/gte.4kscore3631. Published 2022. Accessed 3/20/2026.
14. ECRI. 4Kscore Test (BioReference Laboratories) for Assessing Risk of Aggressive Prostate Cancer before Initial or Repeat Biopsy. https://members.ecri.org/search?k=4Kscore+Test+&page=1&pageSize=20&sort=relevance&dr=false. Published 2018. Accessed 3/20/2026.
15. Konety B, Zappala SM, Parekh DJ, et al. The 4Kscore(R) Test Reduces Prostate Biopsy Rates in Community and Academic Urology Practices. *Rev Urol.* 2015;17(4):231-240.
16. Hayes Inc. ConfirmMDx. https://evidence.hayesinc.com/report/gte.confirm2766. Published 2025. Accessed 3/20/2026.
17. ECRI. ConfirmMDx Test (MDxHealth) for Determining Need for Repeat Prostate Biopsy. https://members.ecri.org/search?k=ConfirmMDx+Test&page=1&pageSize=20&sort=relevance&dr=false. Published 2022. Accessed 3/20/2026.
18. Hayes Inc. PCA3 Detection Test for Prostate Cancer. https://www.hayesinc.com/subscribers/displaySubscriberArticle.do?articleId=10191. Published 2018 (Archived). Accessed 3/20/2026.

19. Tosoian JJ, Druskin SC, Andreas D, et al. Use of the Prostate Health Index for detection of prostate cancer: results from a large academic practice. *Prostate cancer and prostatic diseases.* 2017;20(2):228-233.
20. Hayes Inc. SelectMDx for Prostate Cancer (MDxHealth Inc.). Published 3/21/2019. https://evidence.hayesinc.com/report/gte.selectmdx3769. Published 2024. Accessed 3/20/2026.
21. Inc. H. ExoDx Prostate Test (Exosome Diagnostics Inc.). https://evidence.hayesinc.com/report/mta.exosome5406. Published 2024. Accessed 3/20/2026.
22. ECRI. ExoDx Prostate (IntelliScore; Exosome Diagnostics, Inc.) for Assessing Risk of Aggressive Prostate Cancer. https://members.ecri.org/search?k=ExoDx+Prostate&page=1&pageSize=20&sort=relevance&dr=false. Published 2023. Accessed 3/20/2026.
23. Hayes Inc. Decipher Prostate Cancer Classifier. https://evidence.hayesinc.com/report/gte.decipher4623. Published 2021. Accessed 3/15/2022.
24. Badani KK, Thompson DJ, Brown G, et al. Effect of a genomic classifier test on clinical practice decisions for patients with high-risk prostate cancer after surgery. *BJU Int.* 2015;115(3):419-429.
25. Michalopoulos SN, Kella N, Payne R, et al. Influence of a genomic classifier on post-operative treatment decisions in high-risk prostate cancer patients: results from the PRO-ACT study. *Curr Med Res Opin.* 2014;30(8):1547-1556.
26. Nguyen PL, Shin H, Yousefi K, et al. Impact of a Genomic Classifier of Metastatic Risk on Postprostatectomy Treatment Recommendations by Radiation Oncologists and Urologists. *Urology.* 2015;86(1):35-40.
27. Hayes Inc. Oncotype DX Genomic Prostate Score (GPS) Assay (Genomic Health Inc.). https://evidence.hayesinc.com/report/gte.oncotype2948. Published 2024. Accessed 3/20/2026.
28. Badani KK, Kemeter MJ, Febbo PG, et al. The impact of a biopsy based 17-gene genomic prostate score on treatment recommendations in men with newly diagnosed clinically prostate cancer who are candidates for active surveillance. *Urology Practice.* 2015;2(4):181-189.
29. Dall'Era MA, Maddala T, Polychronopoulos L, Gallagher JR, Febbo PG, Denes BS. Utility of the Oncotype DX® prostate cancer assay in clinical practice for treatment selection in men newly diagnosed with prostate cancer: a retrospective chart review analysis. *Urology Practice.* 2015;2(6):343-348.
30. Hayes Inc. Oncotype DX AR-V7 Nucleus Detect (Epic Sciences). https://evidence.hayesinc.com/report/mta.oncotypedxarv74857. Published 2023. Accessed 3/20/2026.
31. Sharp A, Welti JC, Lambros MB, et al. Clinical utility of circulating tumour cell androgen receptor splice variant-7 status in metastatic castration-resistant prostate cancer. *European urology.* 2019.
32. Armstrong AJ, Halabi S, Luo J, et al. Prospective multicenter validation of androgen receptor splice variant 7 and hormone therapy resistance in high-risk castration-resistant prostate cancer: the PROPHECY study. *Journal of Clinical Oncology.* 2019;37(13):1120-1129.
33. Hayes Inc. Prolaris Biopsy Test (Myriad Genetic Laboratories Inc.). https://evidence.hayesinc.com/report/gte.prolaris2651. Published 2022. Accessed 3/20/2026.
34. Shore ND, Kella N, Moran B, et al. Impact of the Cell Cycle Progression Test on Physician and Patient Treatment Selection for Localized Prostate Cancer. *J Urol.* 2016;195(3):612-618.
35. Crawford ED, Scholz MC, Kar AJ, et al. Cell cycle progression score and treatment decisions in prostate cancer: results from an ongoing registry. *Curr Med Res Opin.* 2014;30(6):1025-1031.

36. Albala D, Kemeter MJ, Febbo PG, et al. Health Economic Impact and Prospective Clinical Utility of Oncotype DX® Genomic Prostate Score. *Reviews in Urology.* 2016;18(3):123-132.
37. National Institute for Health and Care Excellence (NICE). Prostate Cancer: Diagnosis and Management. https://www.nice.org.uk/guidance/ng131. Published 2019. Accessed 3/20/2025.
38. Eastham JA, Auffenberg GB, Barocas DA, et al. Clinically Localized Prostate Cancer: AUA/ASTRO Guideline, Part I: Introduction, Risk Assessment, Staging, and Risk-Based Management. *Journal of Urology.* 2022;208(1):10-18.
39. National Comprehensive Cancer Network (NCCN). Prostate Cancer. Version 5.2026. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Published 2026. Accessed 3/20/2026.
40. National Comprehensive Cancer Network (NCCN). Prostate Cancer Early Detection. Version 2.2026. https://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf. Published 2025. Accessed 3/20/2026.
41. Eggener SE, Rumble RB, Beltran H. Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline Summary. *JCO Oncology Practice.* 2020;16(6):340-343.

POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
5/2023	Changed denial for non-covered services from “investigational” to “not medically necessary.”
6/2023	Changed criteria for Oncotype DX Prostate to allow for unfavorable intermediate and high-risk prostate cancer; Combined criteria I-III; Added PanGIA Prostate to list of non-covered panels.
7/2023	Q3 20023 code update, one expired code, one panel name change
10/2023	Q4 2023 code update
1/2024	Q1 2024 code update.
7/2024	Annual review. Policy title change. CPT code added for PanGIA Prostate testing. Criterion added for repeat testing. Q3 2024 code set update.
8/2024	Interim update. Criteria expansion to include additional NCCN recommended tests.
10/2024	Q3 2024 code set update.
4/2025	Q2 2025 code set update. Interim update to medical necessity criteria.
5/2025	Annual review. No changes to codes or criteria.
7/2025	Q3 2025 code set update. Added code.
10/2025	Q4 2025 code set update. Added code.
1/2026	Interim update. Criteria clarification on NCCN guidelines. Q1 2026 code set update.
7/2026	Annual review. Updated lists of tests in criteria per NCCN update.