MEDICAL POLICY

Medical Policy Title	**Laboratory Testing for the Screening and Management of Prostate Cancer**
Policy Number	**2.02.48**
Current Effective Date	**September 17, 2026**
Next Review Date	**September 2027**

Our medical policies are guides to evaluate technologies or services for medical necessity. Criteria are established through the assessment of evidence based, peer-reviewed scientific literature, and national professional guidelines. Federal and state law(s), regulatory mandates and the member's subscriber contract language are considered first in the determination of a covered service. (Link to Product Disclaimer)

POLICY STATEMENT(S)

Biomarker Testing for Prostate Cancer Screening

I. Biomarker tests for prostate cancer to diagnose or to determine a risk score are considered **investigational**. Including, but not limited to, the following tests:

- A. PROGENSA PCA3 Assay (Prostate Cancer Antigen 3);
- B. 4Kscore;
- C. Prostate Health Index (PHI);
- D. Mitochondrial DNA variant testing (e.g., Prostate Core Mitomics Test);
- E. ConfirmMDx;
- F. Mi-Prostate Score (MiPS);
- G. TMPRSS fusion genes;
- H. PanGIA Prostate;
- I. Apifiny non-PSA blood test (Armune BioScience);
- J. HOXC6 and DLX1 testing (e.g., SelectMDx);
- K. PCA3, ERG, and SPDEF RNA expression in exosomes (e.g., ExoDx Prostate IntelliScore, Exosome Diagnostics, MyProstateScore (MPS), and IsoPSA);
- L. Urine-based advanced small noncoding RNA (sncRNA)interrogation (miR Sentinel); **or**
- M. EpiSwitch PSE.

Management after Prostate Cancer Diagnosis

II. Gene expression analysis to guide the management of prostate cancer, are considered **medically appropriate** when **ALL** of the following criteria have been met:

- A. During initial risk stratification;
- B. Individual has a life expectancy of ten (10) or more years;

C. Individual falls into **ONE (1)** of the disease risk groups below:
   1. For Oncotype DX Genomic Prostate Score (GPS) or ProMark assay:
      a. Low-risk disease; **or**
      b. Favorable intermediate-risk disease.
   2. For Prolaris or Decipher assay:
      a. Low-risk disease;
      b. Favorable intermediate-risk disease;
      c. Unfavorable intermediate disease; **or**
      d. High-risk disease.

III. ArteraAI is considered **investigational** for the management of prostate cancer.

RELATED POLICIES

Corporate Medical Policy

11.01.03 Experimental or Investigational Services

POLICY GUIDELINE(S)

I. Patients should be provided with information about the potential benefits and harms of screening and the limits of the current evidence and should be allowed to make their own decision about screening, in consultation with their physician, based upon personal preferences.

II. The Health Plan and its employees adhere to all State and Federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test or in compliance with applicable law.

III. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.

IV. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.

V. National Comprehensive Cancer Network (NCCN) Recommendations for Prostate Cancer Early Detection: Risk Factors, and Interval for Repeat Testing Grid:

- Guidelines are updated frequently; refer to the source document for current recommendations.

Age/Risk factors	Prostate-Specific Antigen (PSA) (ng/mL)	Repeat Testing Intervals
45-75 yrs. for those with average risk **OR** 40-75 yrs. for individuals with high risk: • Black/African American individuals • Germline mutations that increase the risk for prostate cancer • Suspicious family history	PSA Less than one (1) **AND** Digital Rectal Exam (DRE) normal (if done)	2 to 4 yrs.
	Individuals with high risk and PSA less than or equal to 3 ng/ml, DRE normal (if done) **AND** Individuals with average risk and PSA 1-3 ng/ml, DRE normal (if done)	1 to 2 yrs.
	PSA greater than 3 **AND/OR** DRE is very suspicious	Repeat PSA; workup for benign disease; perform multiparametric MRI if available and consider biomarkers that improve the specificity of screening
Greater than 75 yrs. in select patients If screening continued beyond age 75, perform only with caution in very healthy patients with little to no comorbidity, especially if they have never undergone PSA testing or have increasing PSA levels	PSA less than 4 ng/ml **AND** DRE normal (if done) **AND** no other indications for biopsy	1 to 3 yrs.
	PSA Greater than or equal to 4 ng/ml, **OR** DRE is very suspicious	Same algorithm as individuals ages 40-75 yrs. with PSA greater than three (3) and/or DRE is very suspicious. Repeat PSA; workup for benign disease; perform multiparametric MRI if available and consider biomarkers that improve the specificity of screening
	Not screened	

VI. A tool to estimate life expectancy is the Social Security Administration tables found at: [accessed 2026 Jun 17] Available from: https://www.ssa.gov/OACT/STATS/table4c6.html

VII. NCCN Prostate Cancer Guidelines, Risk Group Chart

Risk Group	Clinical/Pathologic Features	
Low	Has all of the following but does not qualify for very low risk: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL	
Intermediate	Has all of the following: • No high-risk group features. • No very-high-risk group features. Has one or more intermediate risk factors (IRFs): • cT2b–cT2c • Grade Group 2 or 3 • PSA 10–20 ng/mL	Favorable intermediate Has **ALL** of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores • positive (e.g., <6 of 12 cores)
		Unfavorable intermediate Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores • positive (e.g., ≥ 6 of 12 • cores).
High	Has **one or more** high-risk features and has exactly one high-risk feature, but does not meet criteria for very high risk: • cT3-cT4 • Grade Group 4 or Grade Group 5 • PSA >20 ng/mL	
Very High	Has at least two of the following: • cT3–cT4	

	• PSA >40 ng/ml • Grade Group 4 or 5

DESCRIPTION

Prostate cancer is the second most common cancer in the United States with a five-year overall survival of nearly 100% because most prostate cancer diagnosed is a localized disease. Treatment for prostate cancer may include radical prostatectomy, radiation therapy, androgen deprivation therapy, or a combination of any of these treatment options. Research shows that prostate cancer specific mortality is low, with indolent disease often going undiagnosed in patients who die of other causes. Individuals with newly diagnosed prostate cancer can have either aggressive or indolent forms of the disease, and current tools are unable to discriminate between the two. Consequently, all patients are treated as though they have aggressive disease, which leads to overtreatment.

Molecular markers are being actively researched and being proposed as a method for risk-stratifying individuals with prostate cancer to make informed decisions related to biopsy/re-biopsy and treatment.

Biomarkers	**Molecular Markers**
URINE BASED BIOMARKERS	
PCA3 (Progensa)	Prostate cancer antigen 3 (PCA3) is a prostate specific noncoding messenger RNA (mRNA) that has been found to be over expressed in greater than 90% of all prostate tumors compared to that of benign prostatic tissue The PCA3 Score is intended for use in conjunction with standard-of-care diagnostic algorithms as an aid in the diagnosis of prostate cancer.
SelectMDx	The SelectMDx (MDxHealth, Irvine, CA, USA) assay measures the mRNA levels of two genes, HOXC6 and DLX1, that are known to be overexpressed in aggressive prostate cancer. Completed after abnormal PSA and DRE and gives a risk score to guide surveillance.
ExoDx (Intelliscore)	The ExoDx prostate Intelliscore (Exosome Diagnostics Inc., Cambridge, MA, USA) is a non-DRE urine exosome-based assay that measures PCA3 and ERG (Vets erythroblastosis virus E26 oncogene homologs) RNA levels along with a

	control gene, SPEDF. It then combines the molecular markers with SOC (standard of care) variables (PSA, race, age, family history) to delineate the risk of detecting > GGG 2 prostate cancer on biopsy. No DRE needed, provides a risk score before biopsy
MiPs	MiPS (University of Michigan, MLabs) is a post-DRE urine assay which is based on multiplex analysis of T2-ERG fusion, PCA3, and serum PSA (KLK3). Completed after abnormal PSA and DRE and gives a risk score.
PanGIA	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 determine whether a patient should undergo a biopsy. Completed after abnormal PSA and DRE, guides surveillance.
SERUM BASED BIOMARKERS	
4K	Detection of four (4) different kallikrein proteins: total PSA, free PSA, intact PSA, and human kallikrein 2 (hK2). These values are then combined with patient age, DRE results (abnormal or normal), as well as results of prior prostate biopsies to provide a probability score of 0–100% of detecting clinically significant prostate cancer. The 4Kscore test can distinguish men with a low risk of having aggressive prostate cancer on biopsy from those with a high risk.
PHI	Analyzes the levels of free PSA, total PSA and the [−2] form of proPSA (p2PSA). It is calculated by using the following formula: ([−2] proPSA/free PSA) X √ PSA. PHI predicts the likelihood of progression during active surveillance.
TISSUE BASED BIOMARKERS	
Confirm MDx	DNA methylation assay that is prostate tissue biopsy-based. This test evaluates the methylation status of several genes known to be frequently

	found in prostate cancer: Glutathione S-Transferase Pi 1 (GSTP1), Adenomatous Polyposis Coli (APC), and Ras association domain family member 1 (RASSF1). These markers have been demonstrated to have a "field effect," meaning a positive ConfirmMDx test in a cancer negative biopsy suggests that occult cancer was missed during the prostate biopsy. Completed after negative biopsy to guide surveillance.

Gene Expression and Artificial Intelligence Testing for Risk Assessment and Guide in Active Surveillance:

Test name	Description	Used to determine
Genomic Prostate Score (GPS) (Oncotype DX prostate Test)	A multigene reverse transcription polymerase chain reaction (RT-PCR) assay designed to analyze underlying tumor biology in tumor tissue from diagnostic formalin-fixed parafilm-embedded (FFPE) core needle biopsies. The test includes five reference genes and 12 cancer genes representing distinct biological pathways with a known role in prostate tumorigenesis.	The Genomic Prostate Score (GPS) is calculated from the reference normalized expression of the 12 cancer-related genes. The GPS score ranges from 0 to 100 with the higher score reflecting a higher risk.
Prolaris test	A gene expression-based assay that directly measures tumor cell growth characteristics in 31 genes related to cell cycle progression (CCP) and 15 housekeeping genes.	A CCP score is determined which is used to predict 10-year prostate cancer specific disease progression and mortality. CCP scores range from -3.0 to 7.0 with the higher score indicating higher estimated 10-year prostate cancer risk.
Decipher Prostate RP test	Uses the expression of 2 RNA biomarkers involved in multiple biological pathways across the	Calculates the probability of clinical metastasis within five years of radical prostatectomy

Test name	Description	Used to determine
	genome that are associated with aggressive prostate cancer.	surgery.
Decipher Prostate Biopsy test	A whole transcriptome test, utilizes 22 coding and non-coding biomarkers that span seven cancer pathways.	Determines whether the patient should undergo active surveillance, local therapy alone, or multi-modal therapy.
ProMark	Biopsy-based Prostate Cancer prognostic assay that utilizes a multiplex immunofluorescence imaging platform to quantify the values of 8 protein biomarkers demonstrated to be relevant to Prostate Cancer aggressiveness in men with Gleason 3+3 and 3+4 Prostate Cancer.	Biomarker values are incorporated into a risk score (ProMark Score; range: 1-100) indicating the likelihood of having high-risk disease.
ArteraAI	An algorithm assesses digital images from the patient's biopsy and learns from the patient's clinical data.	Biomarkers can predict therapeutic benefit and prognosticate long-term outcomes to enable cancer therapy personalization.

SUPPORTIVE LITERATURE

Kawada et al (2024) conducted a meta-analysis aimed to evaluate the diagnostic accuracy of various multianalyte liquid biomarkers for detecting clinically significant prostate cancer (csPCa) using multiple thresholds. A comprehensive literature search was conducted identifying 49 eligible prospective and retrospective studies. The biomarkers assessed included PCA3, Prostate Health Index (PHI), Four Kallikrein Panel (4K), SelectMDx, ExoDx, and Mi Prostate Score (MPS). Using thresholds determined by the Youden Index, the pooled sensitivity for csPCa detection ranged from 0.82 to 0.87, while specificity ranged from 0.37 to 0.59. The 4K panel demonstrated the highest diagnostic odds ratio (8.84), followed by MPS (7.0) and PHI (6.28). When incorporating multiple thresholds, 4K maintained the highest sensitivity (0.77), while PHI showed the highest specificity (0.72). The findings suggest that 4K offers the best overall diagnostic performance among commercial liquid biomarkers, with PHI being particularly effective in reducing unnecessary biopsies due to its high specificity. The study concludes that while liquid biomarkers are valuable tools for csPCa detection, optimal clinical decision-making should involve a combination of biomarker data and imaging

techniques. Limitations included limited data for newer biomarkers (ExoDx and MPS) and older studies for PCA3 and 4K, and insufficient data for emerging biomarkers (Stockholm3 and circulating immune cells) and therefore were excluded. Another limitation was the difficulty distinguishing between initial and repeat biopsy settings and using the biopsy as a reference standard.

Ross et al (2024) evaluated a multimodal AI (MMAI) model that integrates digital histopathology with clinical data to improve prognostication in patients with high-risk or locally advanced prostate cancer. Using a cohort of 318 patients from the NRG/RTOG 9902 trial, the model was externally validated for its ability to predict distant metastasis (DM) and prostate cancer-specific mortality (PCSM). The MMAI model demonstrated strong, independent associations with both endpoints, with subdistribution hazard ratios of 2.33 for DM and 3.54 for prostate cancer specific mortality (PCSM). The model outperformed traditional clinical risk factors and NCCN high-risk criteria. The findings suggest that MMAI could serve as a valuable tool in clinical decision-making, offering more precise risk stratification to guide treatment planning in high-risk prostate cancer patients.

Spratt et al (2024) presented a novel AI-based approach to personalize treatment for prostate cancer patients. The researchers developed a predictive model using digital pathology images and clinical data from over 5,700 patients across five randomized trials. This model identifies which patients with intermediate-risk prostate cancer are likely to benefit from short-term androgen deprivation therapy (ADT) when combined with radiotherapy. Validation using data from a large clinical trial showed that only 34% of patients were predicted to benefit from ADT, while the remaining 66% did not show significant improvement, suggesting that many patients could avoid unnecessary side effects. The study highlights the potential of AI to guide more precise and effective cancer treatment decisions.

Pchejetski et al (2023) conducted a retrospective case-control study. This study evaluated the diagnostic performance of a combined PSA and Episwitch test—termed the Prostate Screening EpiSwitch (PSE) test—using two cohorts: 109 whole blood samples from the PROSTAGRAM screening pilot study and 38 samples from patients with confirmed PCa and cancer-negative controls from Imperial College NHS Trust. Samples were analyzed for PSA levels and circulating chromosome conformation signatures (CCSs) at loci including DAPK1, HSD3B2, SRD5A3, MMP1, and miRNA98, previously associated with high-risk PCa. PSA testing alone (cut-off >3 ng/mL) yielded a low positive predictive value (PPV) of 0.14 and a high negative predictive value (NPV) of 0.93. The Episwitch test alone demonstrated a PPV of 0.91 and NPV of 0.32. When combined, the PPV improved to 0.81, with a modest reduction in NPV to 0.78. Incorporating PSA as a continuous variable into a multivariate model with Episwitch data resulted in the PSE test, which achieved a PPV of 0.92 and NPV of 0.94 in an independent prospective cohort. The authors found that the test was accurate, rapid, minimally invasive and cost-effective but further validation in a larger, blinded screening cohorts is recommended.

Esteva et al (2022) demonstrated prostate cancer therapy personalization by predicting long-term, clinically relevant outcomes using a multimodal deep learning architecture and train models using clinical data and digital histopathology from prostate biopsies. They trained and validated models using five phase III randomized trials conducted across hundreds of clinical centers. Histopathological data was available for 5,654 of 7,764 randomized patients (71%) with a median follow-up of 11.4 years. Compared to the most common risk-stratification tool-risk groups developed by the National

Cancer Center Network (NCCN)-their models have superior discriminatory performance across all endpoints, ranging from 9.2% to 14.6% relative improvement in a held-out validation set. This artificial intelligence-based tool improves prognostication over standard tools and allows oncologists to computationally predict the likeliest outcomes of specific patients to determine optimal treatment. Outfitted with digital scanners and internet access, any clinic could offer such capabilities, enabling global access to therapy personalization.

Eggener et al (2019), as part of an American Society of Clinical Oncology (ASCO) Multidisciplinary Expert Panel, conducted a systematic literature review of localized prostate cancer biomarker studies between Jan 2013 and 2019. Guidelines with recommendations for available tissue-based prostate cancer biomarkers were developed with a focus on patient selection for active surveillance, identification of clinically significant disease, choice of postprostatectomy adjuvant or salvage radiation therapy (RT), and the value of tissue biomarkers compared to magnetic resonance imaging (MRI). Numerous molecular biomarkers have been developed to improve risk stratification and patient management. Few panels have undergone extensive validation; however, five are commercially available and have been shown in retrospective analyses to provide additional information beyond standard clinical models in prognostication or patient selection for therapy. The authors indicated that, while these tissue-based tests may improve risk stratification when added to standard clinical parameters, their use may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Examples included select patients with high-volume low-risk or favorable intermediate-risk prostate cancer considering active surveillance, and patients with high-risk features for treatment intensification. The authors also noted that, while testing may influence management decisions, there is no high-level evidence to indicate that the results from these panels improve quality of life or cancer-specific outcomes. There have been additional biomarkers evaluated that do not have sufficient data to be clinically actionable or that are not commercially available. Continued investigation of tissue-based molecular biomarkers in the context of clinical trials was recommended.

Knezevic et al (2013) reported the analytical validity of the Oncotype DX Prostate assay. The research showed that the assay could accurately measure expression of the 12 cancer-related and five reference genes over a range of absolute RNA inputs (0.005-320 ng) with a detection limit of 0.05 ng/ml. The analytic accuracy showed average variation of less than 9.7% across all samples at RNA inputs typical of needle biopsy specimens. The amplification efficiency for the 17 genes in the test ranged from 88% to 100%, with a median of 93% (SD=6%) for all 17 genes in the assay. Analytic precision was assessed by examining variability between replicate results obtained using the same messenger RNA level of 5 ng mRNA was used to reflect the lowest 2.5 percentile of a tumor sample of 0.023 cm^3. When converted to GPS units (unit measure for reporting test results), the standard deviation for analytic precision was 1.86 GPS units (95% confidence interval [CI], 1.60 to 2.20) on the 100-unit scale. The standard deviation for reproducibility was 2.11 GPS units (95% CI, 1.83 to 2.50) on the 100-point scale.

PROFESSIONAL GUIDELINE(S)

National Comprehensive Cancer Network (NCCN) Guidelines for Prostate Cancer (V.5.2026) include the following recommendations for tissue-based tests for prostate cancer risk stratification/prognosis.

(NCCN Guidelines are updated frequently; refer to the source document for current recommendations.)

Decipher

Cover post-biopsy for NCCN very-low-, low-risk, favorable intermediate-, and unfavorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy.

Cover post-radical prostatectomy (RP) for:

- pT2 with positive margins;
- any pT3 disease;
- rising PSA (above nadir).

Oncotype Dx Prostate and Prolaris

Cover post-biopsy for NCCN very-low-, low-risk, and favorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy.

Tests that are not recommended:

- KI-67
- PTEN

Multimodal artificial intelligence (MMAI) (ArteraAI Prostate)

"Specific MMAI cut points have not been published to date to precisely guide specific treatment decisions. Rather, the test maybe used to provide more accurate risk stratification to enable improved shared decision-making."

NCCN Guidelines for Prostate Cancer Early Detection (V.2.2026) include the following recommendations to help refine which patients should consider biopsies, with the hopes of decreasing unnecessary biopsies, and increasing specificity of cancer detection:

- “These tests should not be used in place of mpMRI.”
- “The extent of validation of these tests varies across diverse populations and is mostly limited to retrospective observational studies, often funded with industry support. There is a risk of using biomarker tests that lack robust validation to change management decisions.”
- Biomarker tests should meet the following criteria to be included in NCCN guidelines:
    - Validated in a patient cohort that is representative of the intended-use population, ideally in a multi-site, prospective, external validation study or multiple single-site studies.
    - Studies should clearly and transparently describe the eligible patient population and how patients were selected for the study.

  - Validation study or studies should be appropriately powered to achieve statistical significance (on the order of hundreds of patients or more, rather than tens of patients).
  - Study populations should ideally reflect the racial and ethnic diversity of the target population, and studies should report racial and ethnic composition.
  - Validation studies should report number of patients with clinically significant or insignificant prostate cancer and the number of biopsies performed in individuals with the test above a specific test cut-off compared to without test. Reports of receiver operating characteristic (ROC) and area under the curve (AUC) measures alone are not adequate, because these measures are difficult to interpret and they do not describe performance in relation to any specific clinical cut-off.

- 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: Tools 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.
- For the above tests, the panel states that they can be considered in certain circumstances while also encouraging researchers to perform randomized controlled trials that validate the safety and efficacy of biomarker tests; that compare biomarker tests to mpMRI; and that compare biomarker tests head-to-head.

ASCO Guideline (2020) for Molecular Biomarkers in Localized Prostate Cancer is as follows:

- "In patients with prostate cancer who are most likely to benefit from active surveillance: Commercially available molecular biomarkers (Oncotype Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situation in which the assay results, when considered with routine clinical factors, is likely to affect management." (Type: Evidence based; Evidence quality: Intermediate; Recommendation: Moderate).
- "To diagnose clinically significant prostate cancer: Commercially available molecular biomarkers (i.e., Oncotype Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers was not recommended." (Type: Evidence based; Evidence quality: Intermediate; Recommendation: Moderate).
- "To guide the decision for adjuvant or salvage radiation postprostatectomy: The Expert Panel recommends consideration of a commercially available molecular biomarker (e.g., Decipher) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect 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).
- "Comparative strengths and weaknesses of genomics or MRI in identifying clinically significant

prostate cancer: In patients with newly diagnosed prostate cancer who are eligible for active surveillance, both MRI and genomics are intended to identify clinically significant cancers. Their use is endorsed only in situations in which the result, when considered with routine clinical factors, is likely to affect management. This may include, for instance, the initial management of patients who are potentially eligible for active surveillance, where each of these approaches may provide clinically relevant and actionable information. These tests may provide information independent of routine clinical parameters and independent of one another." (Type: Informal consensus; benefits/harms ratio unknown; Evidence quality: Low; Strength of recommendation: Weak) (Eggener et al 2019).

REGULATORY STATUS

The United States Food and Drug Administration (FDA) approved the PSA test for use with the DRE to help detect prostate cancer in individuals aged 50 or older and to monitor patients with a history of prostate cancer.

The FDA indications for use of fPSA state the test is used along with a DRE and tPSA for individuals aged 50 years or older who have a PSA level between 4–10 ng/mL and a prostate gland that appears of normal size and texture.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service. Laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA).

Laboratories that offer laboratory-developed tests must be licensed by CLIA for high-complexity testing. More information is available at: Clinical Laboratory Improvement Amendments (CLIA) | FDA [accessed 2026 Aug 19]

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

CPT Codes

Code	Description
81313 (E/I)	PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (e.g., prostate cancer)
81539 (E/I)	Oncology (high-grade prostate cancer), biochemical assay of four proteins (total PSA, free PSA, intact PSA, and human Kallikdrein-s[HK-2]), utilizing plasma or serum prognostic algorithm reported as a probability score (e.g., 4K Score)

Code	Description
81541	Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score (Prolaris® Assay)
81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score (Decipher Prostate Cancer Assay)
81551 (E/I)	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 (Confirm MDx, MDx Health)
81479 (E/I)	Unlisted molecular pathology procedure
0005U (E/I)	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score (ExosomeDx® Prostate (IntelliScore), Exosome Diagnostics, Inc)
0021U (E/I)	Oncology (prostate), detection of 8 autoantibodies (ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporon, Desmocollin, AURKAIP-1, CSNK2A2), multiplexed immunoassay and flow cytometry serum, algorithm reported as risk score (Apifiny, Armune BioScience, Inc)
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 Genomic Prostate Score (GPS) Test, MDxHealth)
0113U (E/I)	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 (MyProstateScore, Lynx DX)
0228U (E/I)	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 (PanGIA Prostate, Genetics Institute of America, Entopsis, LLC).

Code	Description
0339U (E/I)	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 (SelectMDx for Prostate Cancer, MDxHealth, Inc)
0343U (E/I)	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 (miR Sentinel Prostate Cancer Test, miR Scientific, LLC)
0359U (E/I)	Oncology (prostate cancer), analysis of all prostate-specific antigen (PSA) structural isoforms by phase separation and immunoassay, plasma, algorithm reports risk of cancer (IsoPSA, Cleveland Diagnostics)
0376U (E/I)	Oncology (prostate cancer), image analysis of at least 128 histologic features and clinical factors, prognostic algorithm determining the risk of distant metastases, and prostate cancer-specific mortality, includes predictive algorithm to androgen deprivation-therapy response, if appropriate (ArteraAI Prostate Test, Artera Inc)
0403U (E/I)	Oncology (prostate), mRNA, gene expression profiling of 18 genes, first-catch urine, algorithm reported as percentage of likelihood of detecting clinically significant prostate cancer (MyProstateScore 2.0, LynxDx)
0424U (E/I)	Oncology (prostate), exosome-based analysis of 53 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as no molecular evidence, low-, moderate- or elevated-risk of prostate cancer (miR Sentinel Prostate Test, miR Scientific LLC)
0433U (E/I)	Oncology (prostate), 5 DNA regulatory markers by quantitative PCR, whole blood, algorithm, including prostate-specific antigen, reported as likelihood of cancer (Episwitch Prostate Screening Test, Oxford BioDynamics Inc.)
0495U (E/I)	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 (Stockholm3, BioAgilytix Diagnostics)

Code	Description
0497U (E/I)	Oncology (prostate), mRNA gene expression profiling by real time RT PCR of 6 genes (FOXM1, MCM3, MTUS1, TTC21B, ALAS1, and PPP2CA), utilizing formalin fixed paraffin embedded (FFPE) tissue, algorithm reported as a risk score for prostate cancer (OncoAssure Prostate, Diacarta, Inc)
0591U (E/I)	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 (MiCheck Prostate, Minomic, Inc)
0534U (E/I)	Oncology (prostate), microRNA, single-nucleotide polymorphisms (SNPs) analysis by RT-PCR of 32 variants, using buccal swab, algorithm reported as a risk score (PROSTOX ultra, MiraDx, Inc)
0572U (E/I)	Oncology (prostate), high-throughput telomere length quantification by FISH, whole blood, diagnostic algorithm reported as risk of prostate cancer (ProsTAV, Life Length S.L)
0609U (E/I)	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 (Effective 01/01/26) (ClarityDX Prostate, Protean BioDiagnostics, Nanostics Inc.)

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HCPCS Codes

Code	Description
Not Applicable	

ICD10 Codes

Code	Description
C61	Malignant neoplasm of prostate
D07.5	Carcinoma in situ of prostate
D29.1	Benign neoplasm of prostate
D40.0	Neoplasm of uncertain behavior of prostate

Code	Description
N42.30	Unspecified dysplasia of prostate
N42.31	Prostatic intraepithelial neoplasm
N42.32	Atypical small acinar proliferation of prostate
N42.39	Other dysplasia of prostate
R97.20	Elevated prostate specific antigen (PSA)
R97.21	Rising PSA following treatment for malignant neoplasm of prostate
Z12.5	Encounter for screening for malignant neoplasm of prostate
Z85.46	Personal history of malignant neoplasm of prostate

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SEARCH TERMS

Not Applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Prostate Cancer Screening Tests (NCD 210.1) [accessed 2026 Jun 17]

LCD - Molecular Pathology Procedures (L35000) [accessed 2026 Jun 17]

MolDX: Prostate Cancer Genomic Classifier Assay for Men with Localized Disease (LCD L38339) [accessed 2026 Jun 17]

Gene expression analysis for prostate cancer is not addressed in National or Regional Medicare coverage determinations or policies.

However, please refer to the Medicare Managed Care Manual/Chapter 4: Benefits and Beneficiary Protections (Rev.121, Issued: 04-22-16)/Section 90 National and Local Coverage Determinations/Subsection 90.4.1 MAC with Exclusive Jurisdiction over a Medicare Item or Service:

In some instances, one Medicare A/B MAC processes all of the claims for a particular Medicare-covered item or service for all Medicare beneficiaries around the country. This generally occurs when there is only one provider of a particular item or service (for example, certain pathology and lab tests furnished by independent laboratories). In this situation, MA plans must follow the coverage policy reflected in an LCD issued by the A/B MAC that enrolled the provider and processes all the Medicare claims for that item or service.

https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs-Items/CMS019326 [accessed 2026 June 17]

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.

- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, medical policy criteria apply to the benefit.
- If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.
- If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.
- If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.

POLICY HISTORY/REVISION	
Committee Approval Dates	
08/20/15, 12/15/16, 02/15/18, 12/20/18, 12/19/19, 02/18/21, 12/16/21, 12/22/22, 09/21/23, 09/19/24, 09/18/25, 09/17/26	
Date	**Summary of Changes**
09/17/26	• Annual review; policy intent unchanged.
12/29/25	• Code edit. Added 0609U. Deleted 0550U. Policy intent unchanged.
09/18/25	• Annual review. Policy statements removed regarding PSA, DRE, and PAP as codes are no longer managed and it is considered standard of care. Added investigational code 0591U.
01/01/25	• Summary of changes tracking implemented.
08/20/15	• Original effective date