MEDICAL POLICY

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MEDICAL POLICY DETAILS	
Medical Policy Title	**Laboratory Testing for the Screening and Management of Prostate Cancer**
Policy Number	**2.02.48**
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Product Disclaimer	• *Services are contract dependent; if a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), 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 STATEMENT

Screening

I. New York State Law requires that Health Plan contracts, which provide medical coverage, that includes coverage for physician's services in a physician's office or provides major medical or similar comprehensive-type coverage shall provide, upon the prescription of a health care provider legally authorized to prescribe under the NYS Education Law, the following coverage for diagnostic screening for prostate cancer.
   A. Standard diagnostic testing including, but not limited to, a digital rectal exam (DRE) and Prostate-Specific Antigen (PSA) test at any age for individuals having a prior history of prostate cancer; and
   B. An annual standard diagnostic examination including, but not limited to, a DRE and PSA test for individuals aged 50 and over who are asymptomatic and for individuals aged 40 and over with a family history of prostate cancer or other prostate cancer risk factors.

II. Based upon our criteria and lack of the peer-reviewed literature, screening for prostate cancer with prostatic acid phosphatase (PAP) test is considered **not medically necessary** since the sensitivity of the PSA test has been determined to be superior.

Biomarker Testing for Prostate Cancer Screening

III. Based upon our criteria and the lack of peer-reviewed literature, specific biomarker tests for prostate cancer to diagnosis or to determine a risk score have not been proven medically effective and, therefore, 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); or
L. Urine-based advanced small noncoding RNA (sncRNA)interrogation (miR Sentinel).

Management After Prostate Cancer Diagnosis

IV. Based upon our criteria and assessment of the peer-reviewed literature, gene expression analysis to guide the management of prostate cancer, using the following tests are considered **medically appropriate** during initial risk stratification, when the individual has a life expectancy of ten (10) or more years, and who fall into one (1) of the disease risk groups below:
   A. Oncotype DX Genomic Prostate Score (GPS), and ProMark assay:
      1. Low-risk disease; or
      2. Favorable intermediate-risk disease.
   B. Prolaris or Decipher assay:
      1. Low-risk disease;
      2. Favorable intermediate-risk disease;
      3. Unfavorable intermediate disease; or
      4. High-risk disease.

V. Based upon our criteria and the lack of peer-reviewed literature, ArteraAI has not been medically proven to be effective and, therefore, is considered **investigational** for the management of prostate cancer.

Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services

POLICY GUIDELINES

I. National Comprehensive Cancer Network (NCCN) recommendations for Prostate Cancer Early Detection: Risk factors, and interval for repeat testing.

Age/Risk factors	**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** 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	PSA less than 4 ng/ml **AND** DRE normal (if done) **AND** no other indications for biopsy	1 to 2 yrs.

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 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	

II. A tool to estimate life expectancy is the Social Security Administration tables found at: https://www.ssa.gov/OACT/STATS/table4c6.html

III. Below is the NCCN Prostate Cancer Guidelines, Risk Group Chart:

Risk Group	Clinical/Pathologic Features	
Very Low	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • <3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core. • PSA density <0.15 ng/mL/g	
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 no very-high-risk features and has exactly one high-risk feature: • cT3a **OR** • Grade Group 4 or Grade Group 5 **OR** • PSA >20 ng/mL	
Very High	Has at least one of the following: • cT3b–cT4 • Primary Gleason pattern 5	

	• 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5

IV. 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.

V. PSA or DRE individually can detect prostate cancers, however, the most sensitive method for early detection of prostate cancer uses both DRE and PSA. Both tests should be employed in a program of early prostate cancer detection.

VI. 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.

VII. 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.

VIII. 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.

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.

Prostate-Specific Antigen (PSA) is a glycoprotein produced primarily by the epithelial cells that line the acini and ducts of the prostate gland. PSA is concentrated in prostatic tissue, and serum PSA levels are normally low. Disruption of the normal prostatic architecture, such as by prostatic disease, allows for greater amounts of PSA to enter the general circulation. Elevated serum PSA levels have become an important marker of prostate pathologies, which include benign prostatic hypertrophy, prostatitis, and especially prostate cancer. The higher the PSA, the more likely cancer may be present. The PSA cutoff of 4 ng/mL is associated with an appreciable number of false-positive findings, which diminishes the test's predictive value and results in unnecessary biopsies for those with benign conditions. Moreover, the use of this cutoff is associated with a false-negative rate of 20% (i.e., approximately 20% of men with diagnosed prostate cancer have PSA levels below 4 ng/mL). It is most commonly used as an adjunct to DRE. Serum total PSA was the only PSA-based test available in early detection programs for prostate cancer. Since then, several PSA derivatives have been developed and proposed to improve the performance of the PSA measurement, thus possibly increasing specificity and decreasing unnecessary biopsies. Benign prostate conditions produce more free PSA (fPSA), whereas cancer produces more of the complexed PSA (cPSA). The free-to-total PSA ratio (fPSA/tPSA) may be a useful measure to be used as an adjunct to PSA testing. The fPSA and cPSA measurements can be used when levels are between 4 and 10 ng/mL to help decide whether a biopsy is needed.

Prostatic acid phosphatase (PAP) is an isoenzyme whose levels are markedly elevated in invasive cancer of the prostate. The PAP test can be utilized in the diagnosis and staging of patients with prostatic carcinoma and in monitoring and following a patient's response to therapy. However, it is rarely used since the PSA test has been proven to be more sensitive than the PAP test.

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 for short- and long-term outcomes, and guide in active surveillance decision in low risk and favorable intermediate risk individuals:

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 genome that are associated with aggressive prostate cancer.	Calculates the probability of clinical metastasis within five years of radical prostatectomy 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.

RATIONALE

The National Comprehensive Cancer Network (NCCN) Guidelines of relevance to this policy:

Guidelines	Versions	Recommendations
Prostate Cancer Early Detection	V2.2024	• Please see Policy Guidelines section.
Prostate Cancer	V4.2024	• Decipher- should be considered if not previously performed to inform adjuvant treatment if adverse features are found post-Radical Prostatectomy. • Patients with NCCN low, favorable intermediate, unfavorable intermediate, or high-risk disease and life expectancy ≥10 y may consider the use of the following tumor-based molecular assays: Decipher, Oncotype DX Prostate, and Prolaris. • Multi-Modal Artificial Intelligence (MMAI), ArteraAI Prostate (category 1B) has trained and validated multiple AI-derived digital histopathology-based biomarkers from five (5) phase III randomized radiation-based trials. • Given the superior discrimination of the MMAI model for multiple oncologic endpoints over NCCN risk groups, this test may be used to provide more accurate risk stratification to inform shared decision-making regarding absolute benefit from various treatment approaches. Specific score cut points have not been published to date for specific treatment decisions.

The American Urological Association (AUA) states:

- Clinicians should offer regular prostate cancer screening every two to four years to people aged 50 to 69 years. (Strong Recommendation; Evidence Level: Grade A)
- When screening for prostate cancer, clinicians should use PSA as the first screening test. (Strong Recommendation; Evidence Level: Grade A)
- For people with a newly elevated PSA, clinicians should repeat the PSA prior to a secondary biomarker, imaging, or biopsy. (Expert Opinion)
- Clinicians should engage in shared decision making with people for whom prostate cancer screening would be appropriate and proceed based on a person's values and preferences. (Clinical Principle)
- Clinicians may begin prostate cancer screening and offer a baseline PSA test to people between ages 45 to 50 years. (Conditional Recommendation; Evidence Level: Grade B)

- Better options are needed to stratify patients and to confirm the type of prostate cancer so that patients with aggressive disease receive treatment, while those with a more indolent disease may be treated more conservatively and may benefit from active surveillance.
- Does not recommend routine screening in individuals between ages 40 to 54 years at average risk. ~~For~~ individuals younger than age 55 years at higher risk, decisions regarding prostate cancer screening should be individualized based upon risk factors.

The U.S. Preventive Services Task Force (USPSTF) updated their guidelines on Prostate Cancer: Screening (2018) which states:

- For individuals aged 55 to 69 years, the decision to undergo periodic prostate-specific antigen (PSA)–based screening for prostate cancer should be an individual one.
- Before deciding whether to be screened, individuals should have an opportunity to discuss the potential benefits and harms of screening with their clinician and to incorporate their values and preferences in the decision.
- Clinicians should not screen individuals who do not express a preference for screening (Grade C).
- USPSTF recommends against PSA-based screening for prostate cancer in individuals 70 years and older (Grade D).

ASCO guideline 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).

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.

Analytical validity of the Oncotype DX Prostate assay was reported by Knezevic et al. (2013). 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.

The evidence for the Decipher assay in patients who have high-risk prostate cancer after radical prostatectomy includes one study of analytic validity; eight studies using archived samples; seven prospective-retrospective designs; one case-control) examining clinical validity; six decision curve analyses examining indirect evidence for clinical utility; and one prospective decision impact study. Relevant outcomes included overall survival, disease-specific survival, test accuracy, test validity, quality of life, and treatment-related morbidity. The clinical validity of the Decipher assay has been evaluated in samples of patients with high-risk prostate cancer who are undergoing different interventions following radical prostatectomy. Studies reported some incremental improvement in discrimination. However, it is unclear whether there is consistent improved reclassification—particularly to higher risk categories—or whether the test could be used to predict which patients will benefit from radiotherapy.

A number of different manufacturers make PSA test kits. The 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.

Screening for prostate cancer in asymptomatic men can detect tumors at a more favorable stage (disease confined to the prostate), which is theorized to improve survival. Mortality from prostate cancer has decreased, but it has not been established that this event has resulted directly from screening. Because screening may be detecting cancers that would never have caused morbidity or mortality in the host, the value of early detection remains unclear.

Randomized screening trials are in progress both in the USA and Europe to address the relationship between screening and prostate mortality. The specificity of PSA testing is 60% to 70 % when the PSA level is greater than 4.0ng/ml. The evidence from studies that allow a direct comparison of the yields of PSA and DRE suggests that combining both of these tests improve the overall rate of prostate cancer detection when compared to either test alone.

In many of the studies evaluating the utility of additional PSA derivatives, the most useful parameters appeared to be fPSA/tPSA and its derivative, %fPSA, which is calculated as the ratio of fPSA to tPSA, expressed as a percentage. Many of the investigators preferred using %fPSA, which is more easily expressed. The studies found that %fPSA, or fPSA/tPSA, was better at discriminating benign from malignant prostatic disease compared to tPSA alone or the other PSA parameters and did not decrease sensitivity to detect cancer, while improving specificity by decreasing the number of unnecessary or negative biopsies.

A large number of studies evaluated cPSA and/or cPSA-associated parameters, such as the ratio of cPSA to tPSA, or cPSA/tPSA. A specific assay for cPSA has been developed. Prior to its development, cPSA was derived by subtracting fPSA from tPSA.

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. Although NCCN considers ArteraAI a category 1B recommendation, currently the literature is limited.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

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)
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)
84152	Prostate specific antigen (PSA); complexed (direct measurement)
84153	Prostate specific antigen (PSA); total
84154	Prostate specific antigen (PSA); free
84066 **(NMN)**	Phosphatase, acid; prostatic (PAP)
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)

Code	Description
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 (Oncotype Dx Prostate Cancer Assay)
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).
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) *(Effective 01/01/24)*
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.) *(Effective 01/01/24)*
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 *(Effective 10/01/24)*

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 *(Effective 10/01/24)*

HCPCS Codes

Code	Description
G0102	Prostate cancer screening; digital rectal exam
G0103	Prostate cancer screening; prostate specific antigen test (PSA)

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
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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*Key Article

KEY WORDS

EGIR, Prostate-specific antigen, Prostatic acid phosphatase, PAP, PSA, PCA3Plus, PCA3 gene, 4KScore, Prostate Health Index, ConfirmMDx, Prolaris®, Oncotype DX® Prostate, Confirm MDX®, Gene expression analysis for the prostate, ArteraAI.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a National Coverage Determination (NCD) for Prostate Cancer Screening Tests (210.1). Please refer to the following NCD website for Medicare Members:

http:// www.cms.gov/medicare-coverage-database/view/ncd.aspx?NCDId=268 accessed 07/09/24.

There is currently a National Coverage Determination (NCD) for Prostate Specific Antigen (PSA) (190.31). Please refer to the following websites for Medicare Members:

http://www.cms.gov/medicare-coverage-database/view/ncd.aspx?NCDId=152&DocID=190.31 accessed 07/09/24.

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures which includes PCA3 (L3500). Please refer to the following LCD website for Medicare Members:

https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?LCDId=35000&DocID=L35000 accessed 07/09/24.

There is currently a Local Coverage Determination (LCD) for MolDX: Prostate Cancer Genomic Classifier Assay for Men with Localized Disease (L38339). Please refer to the following LCD website for Medicare members: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?LCDId=38339 accessed 07/09/24.

Based on our review, gene expression analysis for prostate cancer management is not addressed in National or Regional Medicare coverage determinations or policies.