

MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	PROSTATE CANCER SCREENING, DETECTION AND MONITORING
Policy Number	10.01.05
Category	Laboratory Tests
Effective Date	11/29/01
Revised Date	12/05/02, 01/22/04, 02/24/05, 12/01/05, 12/07/06, 10/18/07, 01/15/09, 01/21/10, 05/19/11, 04/19/12, 04/18/13, 03/20/14, 04/16/15, 06/16/16, 07/20/17, 08/16/18
Product Disclaimer	<ul style="list-style-type: none"> • 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 product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit. • If a Medicare 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.

POLICY STATEMENT

- I. Based upon our criteria and assessment of the peer-reviewed literature, including the American Cancer Society (ACS) guidelines for prostate cancer screening, standard diagnostic testing using prostate-specific antigen (PSA) for prostate cancer has been medically proven to be effective and therefore **medically appropriate** after an informed decision with a health care provider. This decision should be made after a discussion about the uncertainties, risks, and potential benefits of prostate cancer screening. The discussion regarding screening should take place at
 - A. Age 40 years for men at higher risk (those with several first-degree relative who had prostate cancer at an early age); or
 - B. Age 45 years for men at high risk of developing prostate cancer; including African Americans and men who have a first-degree relative (father, brother, or son) diagnosed with prostate cancer when younger than age 65 years; or
 - C. Age 50 years for men who are at average risk of prostate cancer and are expected to live at least 10 or more years.

After the initial PSA test is determined, the time interval for repeat testing is dependent upon the PSA value. For those men with a PSA of:

 - A. Less than 2.5 ng/ml retesting may be performed every 2 years;
 - B. Greater than or equal to 2.5 ng/ml retesting may be performed yearly.
- II. New York State Law requires that Health Plan contracts which provide medical coverage that includes coverage for physicians 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 and PSA test at any age for men having a prior history of prostate cancer; and
 - B. An annual standard diagnostic examination including, but not limited to, a digital rectal exam and PSA test for men age 50 and over who are asymptomatic and for men age 40 and over with a family history of prostate cancer or other prostate cancer risk factors.
- III. 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
- IV. Based upon our criteria and the lack of peer-reviewed literature, screening for prostate cancer using other tests have not been proven medically effective and are considered **investigational**. These products include, but are not limited to, the following:
 - A. the molecular urine analysis PROGENSA® PCA3 Assay (Prostate Cancer Antigen 3); or
 - B. 4Kscore; or

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- C. Prostate Health Index (PHI).
- D. Candidate gene panels
- E. Mitochondrial DNA variant testing (eg, Prostate Core Mitomics Test™)
- F. Gene hypermethylation testing (eg, ConfirmMDx®)
- G. TMPRSS fusion genes

Refer to Corporate Medical Policy #2.02.48 regarding Gene Expression Analysis for Prostate Cancer Management

Refer to Corporate Medical Policy #2.02.10 regarding Serum Tumor Markers for the Diagnosis and Management of Cancer.

Refer to Corporate Medical Policy # 6.01.06 regarding Transrectal Ultrasound.

Refer to Corporate Medical Policy #11.01.03 regarding Experimental or Investigational Services

POLICY GUIDELINES

- 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. PSA and digital rectal exam (DRE) can each detect cancers not identified by the other. 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.
- III. The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

DESCRIPTION

Prostate cancer is the second leading cause of cancer death in men. Autopsy studies show that approximately 30% of men over age 50 and 50% of men over age 70 have small cancerous lesions in their prostate glands. The vast majority of these cancers will never progress and never cause any harm.

The goal of early detection is to identify patients who have clinically significant prostate cancers (e.g., cancers that are at an early stage when treatment is most likely to be effective) and reduce prostate cancer morbidity and mortality through effective treatment.

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. Measurement of PSA in the blood has been advocated as a screening test for prostate cancer. Normal PSA levels are not well-defined. 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). Age 50 is traditionally the age for starting to consider PSA screening.

Researchers have recognized that high-risk groups such as men with family histories of prostate cancer and African Americans may benefit from screening at an earlier age. It is recommended that baseline values for these individuals be considered at age 40. While estimates of sensitivity are in the range of 70%, the potential value of this test appears to be its simplicity, objectivity, reproducibility, and lack of invasiveness. 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. PSA circulates in the blood as free (fPSA) or bonded to a protein molecule as complexed PSA (cPSA). Total PSA is the sum of the free and bound forms. This is what is measured as the standard PSA test. Benign prostate conditions produce more fPSA, whereas cancer produces more of the

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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 to more precisely stratify patients to assess the need for therapy, the intensity of therapy, and the extent of surveillance required either before or after initial treatment. A prostate cancer specific gene, PCA3 is one such molecular marker that has been investigated as a possible additional tool in the screening, detection, and management of prostate cancer. The PCA3 gene (may also be referred to as DD3) is markedly upregulated in cancerous prostate cells and is not expressed, or expressed only at very low levels in normal or hyperplastic prostatic tissue. The identification of the PCA gene relies on detection of the overexpression of the associated mRNA in blood or urine after a digital rectal examination.

4Kscore Test is a blood test that includes four prostate-specific kallikreins in the blood: Total PSA, Free PSA, Intact PSA, and Human Kallikrein 2 (hK2). The blood test results are combined in an algorithm with patient age, digital rectal exam (nodules, no nodules), and prior negative biopsy (yes, no) to give physicians a personal score for each patient.

Prostate Health Index (phi) is a blood test that combines total, free and [-2]proPSA into a single score. The per cent free PSA is the percentage of PSA circulating in unbound form and is comprised of several different isoforms including [-2]proPSA, which is more specific for prostate cancer than total PSA or free PSA. nodules), and prior negative biopsy (yes, no) to give physicians a personal score for each patient.

Gene hypermethylation testing (eg, ConfirmMDx[®]) ConfirmMDx[®] assesses the methylation status of 3 biomarkers (GSTP1, RASSF1, APC) associated with prostate cancer. ConfirmMDx is intended for use in patients with high-risk factors such as elevated/rising prostate-specific antigen (PSA) or abnormal digital rectal examination (DRE), with a negative or non-malignant abnormal histopathology finding (e.g., atypical cell or high grade prostate intraepithelial neoplasia (HGPIN)) in the previous biopsy, and is being considered for repeat biopsy.

RATIONALE

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 men age 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 men age 50 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.

The Prostate, Lung, Colon, and Ovarian Cancer Screening trial (PLCO) randomized 76,685 men aged 55 to 74 years at 10 U.S. study centers to annual screening (annual PSA for 6 years and DRE for 4 years) or usual care. After 13 years of follow-up, the incidence rate ratio for the screening arm compared to control was 1.12 (95% CI, 1.07-1.17). The investigators did not find a statistically significant difference between the disease-specific mortality rates of the screening group and of the control (RR, 1.09; 95% CI, 0.87-1.36). Despite the impressive sample size, this trial is flawed by

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prescreening and the high contamination rate of 40% to 52% each year in the control group (i.e., 74% of men in the usual care arm were screened at least once). The estimated mean number of screening PSAs (DREs) in the control arm was 2.7 (1.1); this compared to 5.0 (3.5) in the screened arm. In addition, the biopsy rate for those with elevated serum PSA values was relatively low compared to the European trials. The PLCO trial really compared fixed screening versus “opportunistic” screening, and therefore, did not really test the hypothesis that screening with PSA is of value. However, it did show that yearly screening may be of limited value compared to less frequent testing.

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.

The American Cancer Society (ACS) updated their prostate cancer screening guidelines in 2010. The ACS now recommends “that men have a chance to make an informed decision with their health care provider about whether to be screened for prostate cancer. The decision should be made after getting information about the uncertainties, risks, and potential benefits of prostate cancer screening. Men should not be screened unless they have received this information. The discussion should take place at age 50 for men who are at average risk of prostate cancer and are expected to live at least 10 more years. This discussion should take place starting at age 45 men at high risk of developing prostate cancer. This includes African Americans and men who have a first-degree relative (father, brother, or son) diagnosed with prostate cancer at an early age (younger than age 65). The discussion should take place at age 40 for men at even higher risk (those with several first-degree relatives who had prostate cancer at an early age). After this discussion those men who want to be screened should be tested with the prostate specific antigen (PSA) blood test. The digital rectal exam (DRE) may also be done as part of screening. Even after a decision about testing has been made, the discussion about the pros and cons of testing should be repeated as new information about the benefits and risks of testing becomes available. Further discussions are also needed to take into account changes in the patient’s health, values, and preferences”.

In 2018, the NCCN evidence-based Prostate Cancer Early Detection Guideline (v2.2018) was developed for men who have elected to participate in prostate cancer screening. The panel recognized that prostate cancer represents a true spectrum of disease and that not all men diagnosed with prostate cancer require treatment. The panel believes that maximizing the detection of early prostate cancer will increase the detection of both indolent (slower-growing) and aggressive (faster-growing) prostate cancers. The challenge is to minimize immediate treatment (over-treatment) of indolent cancers by accurately characterizing the biology of the detected cancer. The guideline highlights several techniques designed to improve the identification of significant cancer while avoiding the detection of indolent disease. The guidelines are specifically for men opting to participate in an early detection program (after receiving the appropriate counseling on the pros and cons). It is the majority opinion of the Prostate Cancer Early Detection Panel members that there is a growing population of men currently being diagnosed with prostate cancer who can, and should, be monitored for their disease. The guidelines for when to start and stop screening, at what intervals to conduct screening, and when to biopsy were recommended by most panel members, but a consensus was not reached. The guidelines are continuously in a state of evolution, and the panel will incorporate changes based on new evidence and expert opinion and provide a rating of consensus for each recommendation. The NCCN guidelines recommend for men who choose PSA screening, baseline PSA screening should begin at age 45. If the PSA is less than 1.0 ng/mL, repeat the PSA at age 45. If the PSA is less than 1.0 ng/mL, repeat testing at 2- to 4-year intervals is recommended. If the PSA is greater than or equal 1.0 ng/mL, repeat testing at 1- to 2-year intervals is recommended. The panel notes that a younger man on the higher end of PSA (e.g., a 45-year-old man with PSA 0.9 ng/ml) might be screened in 2 years, whereas an older man with a lower PSA might be screened in 4 years. Clinical judgement should be used. Testing above the age of 75 years should be done with caution and only in very healthy men with little or no comorbidity as a large proportion may harbor cancer that would be unlikely to affect their life expectancy, and screening in this population would substantially increase rates of over-detection. The NCCN guidelines recommend consideration of percent free PSA (%fPSA), 4Kscore, and Prostate Health Index (phi) in

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patients with PSA levels greater than 3 ng/ml. Biomarkers that improve the specificity of detection are not, as yet, recommended as first-line screening tests. 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 further define the probability of high-grade cancer. A per cent free PSA less than 10% , PHI greater than 35, or 4KScore (which provides an estimate of the probability of high-grade prostate cancer) are potentially informative in patients who have never undergone a biopsy or after a negative biopsy; a PCA score greater than 35 is potentially informative after a negative biopsy. %fPSA, PHI, 4KScore, PCA3 and Confirm MDx may also be considered for men who have had at least one prior negative biopsy and are thought to be at higher risk. Results of biomarker assays can be complex and should be interpreted with caution. Referral to a specialist should be considered. It should be pointed out that multiparametric MRI is also a consideration in these same patients. Additional discussion by the panel for the 4KScore and Confirm MDx includes the following: the 4KScore can be considered for patients prior to biopsy and for those with prior negative biopsy who are thought to be at higher risk for clinically significant prostate cancer. It is important for patients and their urologist to understand, however that no optimal cut-off threshold has been established for the 4KScore. If a 4KScore test is performed, the patient and his urologist should discuss the results to decide whether to proceed with a biopsy. The panel believes that the ConfirmMDx test can be considered as an option for men contemplating repeat biopsy, because the assay may identify individuals at higher risk of prostate cancer diagnosis on repeat biopsy.

The U.S. Preventive Services Task Force (USPSTF) updated their guidelines on *Prostate Cancer: Screening (2018)* which states: For men 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, men 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. Screening offers a small potential benefit of reducing the chance of death from prostate cancer in some men. However, many men will experience potential harms of screening, including false-positive results that require additional testing and possible prostate biopsy; overdiagnosis and overtreatment; and treatment complications, such as incontinence and erectile dysfunction. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the balance of benefits and harms on the basis of family history, race/ethnicity, comorbid medical conditions, patient values about the benefits and harms of screening and treatment-specific outcomes, and other health needs. Clinicians should not screen men who do not express a preference for screening (Grade C). The USPSTF recommends against PSA-based screening for prostate cancer in men 70 years and older (Grade D).

A review of the literature specifically in regard to the prostatic acid phosphatase test did not identify any recent studies that were published addressing the use of the test for screening. No mention is made of the PAP test in the recommendations of the applicable specialty societies for prostate cancer screening.

The Gen-Probe PROGENSA® PCA3 Assay was approved by the FDA on February 15, 2012 through the premarket approval process. According to the company's press release, this assay is "indicated for use in conjunction with other patient information to aid in the decision for repeat biopsy in men 50 years of age or older who have had one or more previous negative prostate biopsies and for whom a repeat biopsy would be recommended by a urologist based on the current standard of care, before consideration of PROGENSA PCA3 assay results." The Prostate Health Index was approved by the FDA on June 25, 2012 through the premarket approval process for men with serum PSA values between 4 and 10 ng/ml. The 4KScore test is considered a Laboratory Developed Testing through one CLIA-accredited testing laboratory in Nashville, TN.

An autoantibody serum (phage-protein microarray) test is being studied for the detection of prostate cancer. A retrospective validation study of 257 blood samples from 199 patients with prostate cancer and 138 controls was published September 2005. The study concluded that autoantibodies against peptides derived from prostate-cancer tissue could be used as the basis for a screening test for prostate cancer. Authors stated this assay has not yet been tested for screening and requires confirmation in community-based cohorts

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.*

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- Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

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 Kallidrein-s[HK-2]), utilizing plasma or serum prognostic algorithm reported as a probability score (e.g., 4K Score)
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)

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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
Z80.42	Family history of 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, Confirm MDx

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a National Coverage Determination (NCD) for Prostate Cancer Screening Tests. Please refer to the following NCD website for Medicare Members: <http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=268&ncdver=2&bc=AgAAgAAAAAAA&>

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

NCD: <http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=152&ncdver=1&bc=AgAAgAAAAAAA&>

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures which includes PCA3. Please refer to the following LCD website for Medicare Members: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ver=49&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=Active&bc=AggAAAQIAAAAA%3d%3d&

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There is currently a Local Coverage Determination (LCD) for Biomarker Testing (Prior to Initial Biopsy) for Prostate Cancer Diagnosis. Please refer to the following LCD website for Medicare Members:

https://www.cms.gov/medicarecoverage/database/details/lcddetails.aspx?LCDId=37733&ContrId=298&ver=4&ContrVer=1&CtrctrSelected=298*1&Ctrctr=298&s=41&DocType=All&bc=AAgAAAQAAAA&