

**SUBJECT: 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**

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- *If the member's subscriber contract excludes coverage for a specific service it is not covered under that contract. In such cases, medical policy criteria are not applied.*
- *Medical policies apply to commercial and Medicaid products only when a contract benefit for the specific service exists.*
- *Medical policies only apply to Medicare products when a contract benefit exists and where there are no National or Local Medicare coverage decisions for the specific service.*

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:

- Age 40 years for men at higher risk (those with several first-degree relative who had prostate cancer at an early age); or
- 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
- 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:

- Less than 2.5 ng/ml retesting may be performed every 2 years;
- 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:

- 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
- 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 such as, but not limited to the molecular urine analysis PROGENSA® PCA3 Assay (Prostate Cancer Antigen 3), the autoantibody serum (phage-protein microarray) test, or the prostate skin test (e.g. epidermal genetic information retrieval or EGIR) have not been medically proven to be effective and are considered **investigational**.

The use of transrectal ultrasound (TRUS) of the prostate, as a primary screening tool for prostate cancer, is not supported by the scientific literature and is not addressed in this policy. Please refer to Corporate Medical Policy # 6.01.06 regarding Transrectal Ultrasound.

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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.

Refer to Corporate Medical Policy #11.01.12 regarding Screening Tests.

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 Employees 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 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.

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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.

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.

A prospective randomized controlled clinical trial of 5,855 men from the ongoing European Randomized Screening for Prostate Cancer study evaluated the accuracy of using a PSA-dependent screening interval, concluded that individualized retesting intervals depending on the baseline PSA measurement could be recommended. Men with low PSA values do not need close surveillance and could be spared unnecessary tests and visits. Men with a baseline PSA level of less than 1.99 ng/mL may safely wait 3 years until their next PSA test, while men with a value exceeding 1.50 ng/mL will need annual 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.

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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".

The NCCN 2012 evidence-based Prostate Cancer Early Detection Guideline was developed for men who have elected to participate in prostate cancer screening. The authors state that their guidelines are not designed to address the controversy over whether to screen for prostate cancer. The NCCN developed algorithms for prostate cancer detection. All the recommendations are category 2 B, which means there is uniform NCCN consensus, based on lower level evidence, including clinical experience, that the recommendation is appropriate. The NCCN guidelines recommend for men who choose PSA screening, baseline PSA screening should begin at age 40. If the PSA is less than 1.0 ng/mL, repeat the PSA at age 45. If at age 45 the PSA is less than or equal to 1.0 ng/mL, offer regular screening at age 50. If at age 45 the PSA is greater than or equal 1.0 ng/mL, annual follow-up of DRE and PSA is recommended. If at age 40 the PSA is greater than or equal to 1.0 ng/mL, or African-American, or family history, do annual follow-up of DRE and PSA. If the PSA is greater than 1.0 ng/ml annual follow up of DRE or PSA is recommended. The NCCN guidelines recommend the use %fPSA or cPSA as an alternative in the management of patients with normal DREs and tPSA levels between 4 and 10 ng/mL if there is a contraindication to biopsy. Level 1 evidence is now available from results released through the European Randomized Study of Screening for Prostate Cancer (ERSPC), which evaluated the effect of prostate-specific antigen (PSA) testing on death rates from prostate cancer. During a median follow-up of 9 years, the cumulative incidence of prostate cancer was 8.2% in the screening group and 4.8% in the control group. There were 214 prostate cancer deaths in the screening group, and 326 in the control group. The rate ratio for death from prostate cancer in the screening group, compared to the control group, was 0.80 (95% confidence interval [CI], 0.65-0.98; adjusted P=0.04). The researchers concluded that PSA-based screening reduced the rate of death from prostate cancer by 20%. However they also concluded that this was associated with a high risk of over-diagnosis. Statistically, 1,410 men would need to be screened and 48 men would need to be treated to prevent one death from prostate cancer.

The U.S. Preventive Services Task Force (USPSTF) 2012 statement on prostate cancer screening recommends against prostate-specific antigen-, or PSA-, based screening for prostate cancer in asymptomatic men. The USPSTF discourages use of the PSA for screening because there is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits (Class D recommendation) . The USPSTF concluded that after about 10 years, PSA-based screening results in small or no reduction in prostate-cancer-specific mortality and is associated with harms related to subsequent evaluation and treatments, some of which may be unnecessary.

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."

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.

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CODES: Number Description

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).

<u>CPT:</u>	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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<u>HCPCS:</u>	G0102	Prostate cancer screening; digital rectal exam
	G0103	Prostate cancer screening; prostate specific antigen test (PSA)
	S3721 (E/I)	Prostate cancer antigen 3 (PCA3) testing

<u>ICD9:</u>	V10.46	Personal history of malignant neoplasm of the prostate
	V76.44	Special screening for malignant neoplasm of the prostate
	185	Malignant lesion of the prostate
	222.2	Neoplasm, prostate
	233.4	Carcinoma in situ, prostate
	236.5	Neoplasm of uncertain behavior, prostate

<u>ICD10:</u>	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
	Z12.5	Encounter for screening for malignant neoplasm of prostate
	Z85.46	Personal history of malignant neoplasm of prostate

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KEY WORDS:

EGIR, Prostate-specific antigen, Prostatic acid phosphatase, PAP, PSA, PCA3Plus, PCA3 gene.

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=AgAAGAAAAAA&>

There is currently a National Coverage Determination (NCD) and Local Coverage Determination (LCD) 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=AgAAGAAAAAA&>

LCD: http://apps.ngsmedicare.com/lcd/LCD_L27357.htm

There is currently a Local Coverage Determination (LCD) for Acid Phosphatase. Please refer to the following LCD website for Medicare Members: http://apps.ngsmedicare.com/lcd/LCD_L25879.htm