# Prostate-Specific Antigen Screening for Prostate Cancer



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## DESCRIPTION

Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer deaths in American individuals. In 2022, it is estimated that 268,490 individuals will be diagnosed with prostate cancer and 34,500 will die of this disease. During the same period, individuals in the United States will be confronted with important decisions regarding early detection for prostate cancer. Individuals born in the United States have about 1 chance in 9 of eventually being diagnosed with this malignancy and about 1 chance in 41 of eventually dying of it.

Individuals with Black/African American identity and those individuals with a first-degree relative with prostate cancer (especially cancer found at a younger age) have a higher-risk of developing prostate cancer.

Prostate cancer represents a spectrum of disease that ranges from non-aggressive, slow growing disease that may not require treatment to aggressive, fast-growing disease that

does require treatment. The goal of screening for prostate cancer is to identify high-risk, localized prostate cancer that can be successfully treated, thereby preventing the morbidity associated with advanced or metastatic prostate cancer. Screening asymptomatic individuals for prostate cancer has become a widespread practice in the United States. Tests used for prostate cancer screening include digital rectal examination (DRE) and serum prostate specific antigen (PSA).

Prostate cancer risk calculators have been developed to estimate an individual's risk for prostate cancer from multiple factors. Common calculators are the Sunnybrook, ERSPC and PCPT based risk calculators. These online tools combine clinical variables including but not limited to age, family history, race, DRE, and PSA, to estimate both the risk for biopsy detectable prostate cancer and the risk for biopsy detectable high grade prostate cancer. Such information potentially allows for more informed decision-making. However, such calculators have not been assessed in randomized controlled trials (RCTs) and cut points of risk associated with reductions in prostate cancer mortality remain unknown. Such calculators have as much value in determining who might not need biopsy as in identifying those at higher risk. The use of risk calculators alone to determine whether a biopsy is indicated is not recommended.

Best evidence supports the use of serum PSA for the early detection of prostate cancer. Still, many experts continue to recommend DRE for screening, as some clinically significant prostate cancer may potentially be missed using serum PSA cut point alone. Studies have consistently shown that prostate cancer cases detected through PSA testing are more often confined to the prostate than those detected solely by DRE. Currently, 81% of prostate cancers are pathologically organ-confined at time of diagnosis.

The value of DRE as a stand-alone test for prostate detection is limited, even though DRE picks up some cases of advanced cancer that would otherwise be missed. DRE is recommended to be used as a complementary test with serum PSA in asymptomatic individuals who had a risk/benefit discussion and decided to pursue screening for prostate cancer. Those individuals with a very suspicious DRE should be considered for biopsy referral regardless of PSA results because it may identify high-grade cancers in such situations. DRE should be considered in all individuals with an abnormal serum PSA to aid in decisions regarding biopsy.

Although PSA was originally introduced as a tumor marker to detect cancer recurrence or disease progression following treatment, it became widely adopted for cancer screening. PSA is a glycoprotein produced by the prostate epithelial cells. PSA enters the circulation through unknown mechanisms. PSA levels may be elevated in individuals with prostate cancer because PSA production is increased and because tissue barriers between the prostate gland lumen and the capillary are disrupted, releasing more PSA into the serum. Elevations of serum PSA may also be associated with other prostatic diseases including benign prostatic hypertrophy (BPH) which is a major clinical problem with PSA screening. It is recommended that the interpretation of PSA values should always

consider the following: age, the presence of urinary tract infection or prostate disease, recent diagnostic prostate procedures and prostate directed treatments.

**PSA Derivatives**

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. These PSA derivatives include:

- **Percent free PSA (%fPSA):** Unbound or free PSA (fPSA), expressed as a ratio of tPSA, is a clinically useful molecular form of PSA, with the potential to improve early detection, staging and monitoring of prostate cancer. The FDA approved the use of %fPSA for the early detection of prostate cancer in men with a normal DRE and PSA levels between 4ng/mL and 10 ng/mL.
- **PSA Velocity (PSAV)**: The rate of change in PSA over time is broadly termed PSA velocity (PSAV), determined by at least 3 separate PSA values calculated over at least an 18- month period. PSAV $\geq$ 0.35 ng/mL/y is only one criterion to consider when deciding whether to perform biopsy for men with low PSA levels. Other factors such as age, comorbidity, race, and family history also should be considered. Also, the predictive value of PSAV can be influenced by PSA levels, PSAV is not useful in individuals with a very high > 10 ng/mL PSA values. An abnormal PSA result should be confirmed by retesting.
- **cPSA**: PSA exists in free and several complexed forms. Direct measurement of the complexed form with alpha-1-antichymotrypsin is now available. For practical purposes, tPSA consists essentially of fPSA and the alpha-1-antichymotrypsin complex form (cPSA). The threshold levels are therefore not equivalent: cPSA levels of 2.2 ng/mL and 3.4 ng/mL are equivalent to tPSA levels of 2.5 ng/mL and 4.0 ng/mL, respectively. The ratio of cPSA to tPSA should provide information comparable to the fPSA to tPSA ratio. The use of cPSA has been approved as an aid in the detection of prostate cancer in men aged 50 years or older in conjunction with DRE. However, because cPSA has not gained widespread acceptance in a day-to-day clinical practice, it has not been incorporated into early detection guidelines as a baseline measure.
- **PSA Density (PSAD):** PSAD requires measurement of prostate volume by TRUS and is expressed as the PSA value (in nanograms per milliliter; ng/mL) divided by the prostate volume (in cc, cubic centimeters). PSAD is a means of discriminating prostate cancer from BPH: the lower the PSAD, the greater the probability of BPH. Therefore, PSAD potentially identifies men who do not have prostate cancer but have high PSA secondary to large volume prostates. The lack of precision of measurement of both PSA and prostate volume has prevented the widespread clinical use of PSAD. PSAD has not been incorporated into early detection guidelines as a baseline measure because PSAD alone may offer little added benefit over other tests and requires ultrasound.

Even though some guidelines (i.e., USPSTF) may not recommend the routine use of screening tests for prostate cancer which the benefits do not outweigh the harms in the target population, they do recognize the common use of PSA screening in practice today and that some physicians will continue to offer it. The decision to initiate or continue

PSA screening should reflect an understanding of the possible benefits and harms and respect the individuals's preferences. Physicians should not offer or order PSA screening unless they are prepared to engage in shared decision making that enables an informed choice by the individual. Similarly, individuals requesting PSA screening should be provided with the opportunity to make informed choices to be screened that reflect their values about specific benefits and harms.

Prostate cancer screening has been a controversial issue. There is evidence that PSA based screening leads to substantial over-diagnosis of prostate tumors and there is a high incidence for physicians and individuals to elect to treat most cases of screen detected cancer, given the current inability to distinguish tumors that will remain indolent from those destined to be lethal. Thus, many individuals are being subjected to the harms of treatment of prostate cancer that will never become symptomatic. Even for individuals whose screen-detected cancer would otherwise have been later identified without screening, most experience the same outcome and are, therefore, subjected to the harms of treatment for much longer period. There is convincing evidence that PSA based screening for prostate cancer results in considerable overtreatment and its associated harms.

Despite its limitations, recent population-based prostate cancer screening studies have demonstrated survival benefits using PSA, sometimes in combination with digital rectal examination (DRE).

PSA-based screening for prostate cancer has been studied in 3 very large RCTs, each with at least a decade of median follow-up: the US-based Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, the European Randomized Study of Screening for Prostate Cancer (ERSPC), and the Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP). These trials used varying screening intervals (from 1-time screening to every 1 to 4 years) and PSA thresholds (2.5 to 10.0 ng/mL) for diagnostic biopsy.

In 2018, de Koning et. al. reported on the efficacy of prostate-specific antigen screening and the impact of the key components in the European Randomized Study for Prostate Cancer (ERSPC) and the U.S. Prostate, Lung, Colorectal and Ovarian (PLCO) trials. The European Randomized Study of Screening for Prostate Cancer (ERSPC) demonstrated that prostate-specific antigen (PSA) screening significantly reduced prostate cancer mortality (rate ratio, 0.79; 95% confidence interval, 0.69-0.91). The U.S. Prostate, Lung, Colorectal, and Ovarian (PLCO) trial indicated no such reduction but had a wide 95% CI (rate ratio for prostate cancer mortality, 1.09; 95% CI, 0.87-1.36). Standard meta-analyses are unable to account for key differences between the trials that can impact the estimated effects of screening and the trials' point estimates. The authors calibrated 2 microsimulation models to individual-level incidence and mortality data from 238,936 men participating in the ERSPC and PLCO trials. A cure parameter for the underlying efficacy of screening was estimated by the models separately for each trial. The authors changed step-by-step major known differences in trial settings, including enrollment and

attendance patterns, screening intervals, PSA thresholds, biopsy receipt, control arm contamination, and primary treatment, to reflect a more ideal protocol situation and differences between the trials. Using the cure parameter estimated for the ERSPC, the models projected 19% to 21% and 6% to 8%, respectively, prostate cancer mortality reductions in the ERSPC and PLCO settings. Using this cure parameter, the models projected a reduction of 37% to 43% under annual screening with 100% attendance and biopsy compliance and no contamination. The cure parameter estimated for the PLCO trial was 0. The authors concluded, the observed cancer mortality reduction in screening trials appears to be highly sensitive to trial protocol and practice settings. Accounting for these differences, the efficacy of PSA screening in the PLCO setting is not necessarily inconsistent with ERSPC results.

The potential benefit of screening for prostate cancer is because of treatment. It is important for individuals to consider both the potential benefits and harms of treatment (including surveillance) as they consider whether to be screened. Individuals not able or willing to tolerate treatment should not be screened for prostate cancer.
Most cases of prostate cancer advance very slowly, if at all, the 10- year survival rate for screen-detected, localized prostate cancer is very high. In recent major trial that enrolled more than 1500 men randomized to receive either active treatment or active surveillance, the 10-year survival rate in all groups was 99%. The good prognosis for early- stage prostate cancer makes it difficult to study the effectiveness of treatment.

Multiple treatment options exist for prostate cancer, the three most common treatment options for individuals with screen-detected localized prostate cancer are surgical removal of prostate gland (radical prostatectomy), radiation therapy, and active surveillance. Available evidence on treatment evaluating the effectiveness of screening found that current evidence suggests that treatment of early-stage, screen-detected prostate cancer with radical prostatectomy or radiation therapy likely reduces the risk of clinical progression and metastatic disease and may reduce prostate cancer mortality.

Active surveillance is a treatment approach that seeks to limit the harms of treatment by allowing individuals with apparent low-risk prostate cancer to forego surgery or radiation in favor of ongoing monitoring of their cancer. Although protocols vary, active surveillance usually includes regular, repeated PSA testing and often repeated digital rectal examination (DRE) and prostate biopsy, with the potential for exposure to repeated harms from biopsies. Individuals whose cancer is found to be changing are offered definitive treatment with surgery or radiation therapy. Active surveillance has become a more common treatment choice in the United States over the past several years. Active treatment of prostate cancer can result in major adverse effects.

**Summary of Evidence**
There are several clinical studies identified in the peer-reviewed medical literature that address the impact of PSA screening on the stage of cancer detection and on disease-specific survival rates, as well as studies that evaluate the relative sensitivities and specificities of derivative types of PSA testing. Although PSA testing is widely used

there is controversy regarding the question of whether PSA-based screening reduces prostate cancer mortality. In addition, PSA-based screening is associated with risks of overdiagnosis and overtreatment. The current National Comprehensive Cancer Network Guideline (NCCN) on Prostate Cancer Early Detection (Version 1.2022) states: "factors to consider in the early detection of prostate cancer include the individuals age, life expectancy, race, presence of inherited mutations, family history, and previous results from early detection tests. The NCCN Panel concluded that tailoring screening intervals based on PSA levels might maximize survival advantage while decreasing the number of screenings and limiting overdiagnosis. The Panel members favor informed testing beginning at age 45 years. The Panel recommends repeat testing every 2 to 4 years if PSA is <1 ng/ml and every 1 to 2 years if PSA is 1 to 3 ng/ml in individuals aged 45 to 75 years. Panelists uniformly agreed that PSA testing should only be offered to individuals with a 10 or more-year life expectancy. However, panelists did not agree as to when to discontinue routine testing in asymptomatic older individuals. The primary goal of PSA based screening is to find individuals from whom treatment would reduce morbidity and mortality. Based on the peer reviewed medical literature from randomized clinical trials (RCTs), prostate cancer screening using PSA has at most a small benefit in reducing prostate cancer mortality and the risk of developing metastatic disease. The potential benefits of screening must be balanced against the potential harms to quality of life (QOL).

**Practice Guidelines and Position Statements**

**American Urological Association (AUA)**
In 2013, the American Urological Association (AUA) published guidelines for the early detection of prostate cancer, this guideline was reviewed and validated 2018:

**Guideline Statements**
- The Panel recommends against PSA screening men under age 40 years. (Recommendation; Evidence Strength Grade C). In this age group there is a low prevalence of clinically detectable prostate cancer, no evidence demonstrating benefit of screening and likely the same harms of screening as in other age groups.
- The Panel does not recommend routine screening in men between ages 40 to 54 years at average risk. (Recommendation; Evidence Strength Grade C). For men younger than age 55 years at higher risk (e.g., positive family history or African American race), decisions regarding prostate cancer screening should be individualized. Those at higher risk may include men of African American race; and those with a family history of metastatic or lethal adenocarcinomas (e.g., prostate, male and female breast cancer, ovarian, pancreatic) spanning multiple generations, affecting multiple first-degree relatives, and that developed at younger ages.
- For men ages 55 to 69 years the Panel recognizes that the decision to undergo PSA screening involves weighing the benefits of reducing the rate of metastatic prostate cancer and prevention of prostate cancer death against the known potential harms associated with screening and treatment. For this reason, the Panel strongly recommends shared decision making for men aged 55 to 69 years that are considering

PSA screening and proceeding based on a man's values and preferences. (Standard; Evidence Strength Grade B). The greatest benefit of screening appears to be in men ages 55 to 69 years.

- To reduce the harms of screening, a routine screening interval of two years or more may be preferred over annual screening in those men who have participated in shared decision making and decided on screening. As compared to annual screening, it is expected that screening intervals of two years preserves the majority of the benefits and reduce over-diagnosis and false positives. (Option; Evidence Strength Grade C). Additionally, intervals for rescreening can be individualized by a baseline PSA level.
- The Panel does not recommend routine PSA screening in men over age 70 years or any man with less than a 10- to 15-year life expectancy. (Recommendation; Evidence Strength Grade C).
    - Some men over age 70 years who are in excellent health may benefit from prostate cancer screening.

The panel concluded that PSA based screening should not be performed in the absence of shared decision making. Thus, they recommend against organized screening in settings where shared decision making is not part of routine practice (e.g., including but not limited to health fairs, health system promotions, community organizations).

**Testing Frequency**:
The Panel believes that annual PSA screening as a routine should be discouraged for those who choose to be screened, that two-year PSA intervals are reasonable approach and will be unlikely to miss a curable prostate cancer in most men, and that for men over 60 with PSA levels below 1.0ng/ml, longer PSA screening intervals (e.g., of four years) could be considered. Men with PSA below 3 ng/mL at age 70 to 75 years, PSA screening could be safely discontinued if a man at this age is still being screened.

**The American Cancer Society (ACS)**
In 2021, the American Cancer Society reaffirmed their recommendation that men 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, risk, and potential benefits of prostate cancer screening. Men should not be screened unless they have received this information. The discussion about screening 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.
- Age 45 for 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)
- Age 40 for men at even higher risk (those with more than one first degree relative who had prostate cancer at an early age)

After this discussion 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.

If, after this discussion, a man is unable to decide if testing is right for him, the screening decision can be made by the health care provider, who should take into account the man's general health preferences and values.

If no prostate cancer is found as a result of screening, the time between future screenings depends on the results of the PSA blood test:

- Men who choose to be tested who have a PSA of less than 2.5 ng/mL may only need to be retested every 2 years.
- Screening should be done yearly for men whose PSA level is 2.5 ng/mL or higher.

Because prostate cancer often grows slowly, men without symptoms of prostate cancer who do not have a 10-year life expectancy should not be offered testing since they are not likely to benefit. Overall health status, and not age alone, is important when making decisions about 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 a man's health, values, and preferences.

**National Comprehensive Cancer Network (NCCN)**
**Prostate Cancer Early Detection Version 1.2022**
The panel supports the continued use of prostate-specific antigen (PSA) testing for the early detection of prostate cancer in informed, healthy individuals in certain age groups. The panel basis this recommendation on level I evidence from randomized trials that observed a reduction in prostate cancer-specific mortality in those who underwent PSA screening. However, the panel also uniformly acknowledge the risk of over detection of otherwise indolent disease and the attendant risk of overtreatment which exposes patients to the potential morbidity of treatment without benefit.

The Panel members favor informed testing beginning at age 45 years. The Panel recommends repeat testing every 2 to 4 years if PSA is <1 ng/ml and every 1 to 2 years if PSA is 1 to 3 ng/ml in individuals aged 45 to 75 years. Panelists uniformly agreed that PSA testing should only be offered to individuals with a 10 or more-year life expectancy. However, panelists did not agree as to when to discontinue routine testing in asymptomatic older individuals.

**Baseline Evaluation**
**History and physical including:**

- Family cancer history
- Medications

- History of prostate disease and cancer early detection, including prior PSA and/or isoforms, exams, and biopsies
- Black/African American identity
- Family or personal history of high-risk germline mutations
- Environmental exposure

**Start risk and benefit discussion about offering prostate screening:**

- Baseline PSA
- Strongly consider baseline digital rectal examination (DRE)

**Early Detection Evaluation**

- Age 45-75 years for average risk patients; **or**
- Age 40-75 years for those with:
    - Black/African American individuals
    - Those with germline mutations that increase risk for prostate cancer
    - Those with suspicious family history

PSA < 1 ng/mL, DRE normal if done: repeat testing at 2–4-year intervals
PSA1-3 ng/mL, DRE normal if done: repeat testing at 1–2-year intervals
PSA > 3 ng/mL and/or very suspicious DRE: see indications for biopsy

Black/African American individuals have a higher incidence of prostate cancer, increased prostate cancer mortality, and earlier age of diagnoses compared to Caucasian individuals. This is attributable to a greater risk of developing preclinical prostate cancer and a higher likelihood that a preclinical tumor will spread. Lack of access to care and other social determinates of health are also associated with poor outcomes in this population. There are data suggesting a role for heritable genes linked to Black/African American individuals as drivers of increased risk in this patient population. Many support the recommendation for Black/African American individuals to consider beginning shared decision making about PSA screening at age 40 years and to consider screening at annual intervals rather than every other year. There is no current evidence to support that screening at an earlier age will result in decrease morbidity and mortality compared to testing at age 45, and earlier screening may increase over-diagnosis.

**Age > 75 years in select patients (category 2B)**

- PSA < 4 ng/mL, DRE normal (if done) and no other indications for biopsy: repeat testing in select patients at 1–4-year intervals
- PSA ≥ 4 ng/mL or very suspicious DRE: see indications for biopsy
- Not screened: testing after 75 years of age should be done only in very healthy men with little or no comorbidity (especially if they have never undergone PSA testing) to detect the small number of aggressive cancers that post a significant risk if left undetected until signs or symptoms develop. Widespread screening in this population would substantially increase rates of over-detection and is not recommended.

**U.S. Preventative Services Task Force (USPSTF)**
In 2018, The USPSTF published updated recommendations regarding prostate cancer screening that states the following:

**Men aged 55–69**
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 Recommendation

**Men aged 70 and older**
The USPSTF recommends against PSA-based screening for prostate cancer in men age 70 years and older.
Grade D Recommendation

This recommendation applies to adult men in the general U.S. population without symptoms or a previous diagnosis of prostate cancer. It also applies to men at increased risk of death from prostate cancer because of race/ethnicity or family history of prostate cancer.

# PRIOR APPROVAL

Not applicable.

# POLICY

**See Related Medical Policies**

- 02.04.56 Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer
- 02.04.57 Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

Prostate cancer screening using prostate specific antigen (PSA) may be considered **medically necessary** for any of the following indications after informed decision-making with a health care provider:

- Asymptomatic individuals 40-49 years of age who are at high- risk of prostate cancer due to any of the following factors:
    - Black/African American identity; **or**
    - More than one first degree relative (father, brother, or son) diagnosed with prostate cancer at an early age (younger than age 65); **or**
- Asymptomatic individuals aged 50 and over with a life expectancy of at least 10 years.

After the initial prostate cancer screening using prostate specific antigen (PSA) is determined, the time interval for repeat screening testing using prostate specific antigen (PSA) is dependent upon the prostate specific antigen (PSA) value, which is the following:

- PSA < 1 ng/ml repeat testing may be performed at 2 - 4 -year intervals
- PSA 1-3 ng/ml repeat testing may be performed at 1-2-year intervals

Prostate cancer screening using prostate specific antigen (PSA) not meeting the above criteria in asymptomatic individuals is considered **not medically necessary**.

# PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 84152 Prostate-specific antigen (PSA); complexed (direct measurement)
- 84153 Prostate-specific antigen (PSA); total
- 84154 Prostate-specific antigen (PSA); free
- G0103 Prostate cancer screening, prostate specific antigen test (PSA)

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  Also available at http://www.auanet.org

| POLICY HISTORY | | |
|---|---|---|
| **Date** | **Reason** | **Action** |
| June 2022 | Annual Review | Policy Revised |
| June 2021 | Annual Review | Policy Revised |
| June 2020 | Annual Review | Policy Renewed |
| June 2019 | Annual Review | Policy Renewed |
| June 2018 | Annual Review | Policy Revised |
| June 2017 | Annual Review | Policy Revised |
| June 2016 | Annual Review | Policy Revised |
| December 2015 | Annual Review | Policy Revised |
| February 2015 | Annual Review | Policy Revised |
| March 2014 | Annual Review | Policy Revised |
| April 2013 | Annual Review | Policy Revised |
| February 2013 | Interim Review | Policy Revised |
| April 2012 | Annual Review | Policy Renewed |
| May 2011 | Annual Review | Policy Renewed |

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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