

Corporate Medical Policy

Prostate Specific Antigen (PSA) Testing AHS - G2008

File Name: prostate_specific_antigen_psa_testing
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Description of Procedure or Service

Prostate-specific antigen (PSA) is a glycoprotein that is produced by both normal and neoplastic prostate tissue. In normal conditions, PSA is produced as a proenzyme in the prostate and secreted into the lumen. The propeptide is removed to activate the proenzyme; from there, it undergoes proteolysis to inactivate it. This inactive form may enter the bloodstream and circulate as “free” PSA. This process differs in prostate cancer; the basal cells that normally regulate this activation process are missing, which allows the secreted PSA direct access into the bloodstream. This increases the PSA concentration in the serum (Freedland, 2022).

Due to these reasons, PSA is often used in assessment of prostate cancer, such as screening, monitoring, diagnosis, and treatment management.

Terms such as male and female are used when necessary to refer to sex assigned at birth.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for prostate specific antigen (PSA) testing when it is determined the medical criteria and guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore, member benefit language should be reviewed before applying the terms of this medical policy.

When Prostate Specific Antigen (PSA) Testing is covered

1. Reimbursement is allowed for average-risk individuals 45-75 years of age, screening for prostate cancer with the total prostate-specific antigen (PSA) test.

2. Reimbursement is allowed for individuals 40-75 years of age, annual screening for prostate cancer with the total (PSA) test when one of the following conditions is met:
 - a. Individual is of African ancestry.
 - b. Individual has germline mutations that increase risk for prostate cancer.
 - c. Individual has a suspicious family history.
3. For individuals over 75 years of age who have little or no comorbidities (*See Note 1), reimbursement is allowed for screening for prostate cancer with a total PSA test.
4. For individuals with previous total PSA results, repeat screening for prostate cancer with a total PSA test, reimbursement is allowed with the following frequency:
 - a. For individuals less than 76 years of age, when total PSA is <1 ng/ml and digital rectal exam (DRE) is normal (if done): Repeat screening at 2- 4 year intervals.
 - b. For individuals less than 76 years of age, when total PSA is 1-3 ng/ml and DRE is normal (if done): Repeat screening at 1- 2 year intervals.
 - c. For individuals greater than 75 years of age, when total PSA is <4 ng/ml and DRE is normal (if done) and no other indications for biopsy: Repeat screening in select patients (very healthy individuals with little or no comorbidity) at 1- 4 year intervals.
5. TRUS-guided biopsy, percent free PSA, **or** a follow-up in 6-12 months with total PSA or DRE, reimbursement is allowed when **any** of the following conditions are met:
 - a. For individuals less than 76 years of age with a total PSA >3 ng/ml and/or a very suspicious DRE.
 - b. For select individuals greater than 75 years of age (very healthy individuals with little or no comorbidity) with a total PSA \geq 4 ng/ml or a very suspicious DRE.
6. For individuals thought to be at a higher risk despite at least one prior negative prostate biopsy, follow-up testing with percent free PSA, reimbursement is allowed.
7. Total PSA testing, reimbursement is allowed, in **any** of the following situations:
 - a. For initial prostate cancer diagnosis in individuals with signs and symptoms of prostate cancer (see Note 2).
 - b. For follow-up of individuals with a current or previous diagnosis of prostate cancer.
 - c. For ongoing monitoring of individuals who have undergone tumor resection or prostatectomy.
 - d. For monitoring response to therapy.
 - e. For detecting disease recurrence.

*NOTE 1: According to the NCCN guidelines, “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 or have a rising PSA) to detect the small number of aggressive cancers that pose 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 (NCCN, 2023b).” Additionally, the term individuals in this policy apply to individuals who have a prostate or were born with a prostate.

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*NOTE 2: According to ACS, 2019: “Most prostate cancers are found early, through screening. Early prostate cancer usually causes no symptoms. More advanced prostate cancers can sometimes cause symptoms, such as:

- Problems urinating, including a slow or weak urinary stream or the need to urinate more often, especially at night
- Blood in the urine or semen
- Trouble getting an erection (erectile dysfunction or ED)
- Pain in the hips, back (spine), chest (ribs), or other areas from cancer that has spread to bones
- Weakness or numbness in the legs or feet, or even loss of bladder or bowel control from cancer pressing on the spinal cord (ACS, 2019).

When Prostate Specific Antigen (PSA) Testing is not covered

Reimbursement is not allowed for:

- a. Percent free PSA as a first-line screening test for prostate cancer.
- b. Percent free PSA, free-to-total PSA ratio, and/or complexed PSA tests for the routine screening of prostate cancer.

Policy Guidelines

Prostate cancer is the most common cancer in American men and the second leading cause of death in men over 65 (Balducci et al., 1997; Tabayoyong & Abouassaly, 2015). According to the CDC (2022a), more than 224,000 prostate cancer cases are reported annually in the United States, leading to more than 31,000 prostate cancer deaths each year. The American Cancer Society estimates over 288,000 new cases and 34,000 deaths of prostate cancer in 2023 (American_Cancer_Society, 2023). Prostate cancer survival is related to many factors, especially the extent of the tumor at the time of diagnosis. The 5-year survival rate between for men with localized or regional prostate cancer is nearly 100%, while the 5-year survival rate for men with distant prostate cancer where the cancer has spread to other parts of the body such as the lungs, liver or bones is 31% (ACS, 2022; Hoffman, 2023). About one man in nine will be diagnosed with prostate cancer during his lifetime in the United States (American_Cancer_Society, 2023).

Many cases of prostate cancer do not become clinically evident, as indicated in autopsy studies, where prostate cancer is detected in approximately 30 percent of men aged 55 or older and approximately 60 percent of men by age 80 (Bell et al., 2015). These data suggest that prostate cancer often grows so slowly that most men die of other causes before the disease becomes clinically advanced (Hoffman, 2023).

Most prostate cancers use androgen-dependent signaling for development and progression (Fisher et al., 2015). As the number of targeted therapy agents increase, it is crucial to determine which patients will benefit from these interventions. Understanding the molecular pathology will allow clinicians to provide better patient management. Recent studies have led to the classification of prostate cancer into different subtypes, yet the utility of this in the clinical setting is to be determined (Rodrigues, et al., 2014).

Prostate-specific antigen (PSA), a glycoprotein produced by prostate epithelial cells, is the most widely accepted biomarker for prostate cancer screening. Levels of this protein can be identified via a simple blood test; many doctors consider abnormal PSA levels to be above 4.0 ng/mL, although there is no official standardized normal or abnormal PSA level (NCI, 2022a). Further, PSA levels tend to increase with age, suggesting that age-specific PSA reference ranges may be important for clinical use (NCI, 2022a).

In serum, PSA can be identified in three forms. The main form is PSA bound by alpha-1 antichymotrypsin and accounts for approximately 75% of total PSA; PSA bound to alpha-2 macroglobulin has also been

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identified but cannot be detected by commercial immunoassays and represents less than 0.1% of PSA (Prcic, et al., 2016). Coban et al. (2016) reported that, while total PSA levels are an important prognostic factor for predicting prostate volumes, free PSA levels had a higher predictive value.

Analytical Validity

PSA was originally introduced as a tumor marker to detect cancer recurrence or disease progression following treatment (Brawley et al., 2018). It has been widely adopted for early detection of prostate cancer screening; however, its clinical utility in screening is controversial, and guidelines for PSA screening are conflicting. Non-optimal screening and treatment practices, including excessive screening among older men with lower life expectancy or comorbidities and overtreatment of men with low-risk tumors, have contributed to treatment-related harm and a lower quality of life (Fleshner et al., 2017). Evidence is currently lacking to show that PSA screening actually saves lives; instead, it may only cause overdiagnosis and lead to complications in the treatment of indolent diseases (Ilic et al., 2018).

PSA is not a cancer specific marker, thereby causing many false results that conflict with other screening methods, such as the digital rectal examination (DRE) (Saini, 2016). For example, PSA may be elevated due to conditions including benign prostatic hyperplasia (BPH) or prostatitis. This is particularly important as BPH is common among men over 50, the most common age group in which prostate cancer is observed. For example, a study performed by Stimac et al. (2014) found PSA levels to be unusual despite testing negative for cancer. The authors concluded that subclinical inflammation had a major influence on free PSA levels only if the total levels was <10 ng/mL, and further note that clinical and acute inflammation produce a different profile of PSA release compared to a subclinical inflammation. Overall, the authors state that the molecular cause of the inflammation's changes to PSA forms are still unknown (Stimac et al., 2014). Furthermore, serum PSA is directly tied to the size of the prostate, which increases with age. Older men may see an increased concentration of PSA despite being completely healthy (Freedland, 2022; Stimac et al., 2014). Other factors such as medication can affect PSA levels as well. Common medications such as statins, NSAIDs, acetaminophen, 5-alpha-reductase inhibitors, and thiazides were all found to reduce PSA levels by varying degrees (Chang, et al., 2010; Hamilton, et al., 2008; Singer, et al., 2008; Wang, et al., 1997).

Clinical Validity and Utility

The utility of PSA-based screening is also in question. A randomized clinical trial focusing on men undergoing a single PSA-based screening (n = 189386) compared to controls not undergoing a PSA-based screening (n = 219439) found no difference in cancer mortality after a median follow-up of 10 years. The mortality rate in 1000-person years was 0.30 in the intervention group compared to 0.31 in the control group, or one extra death per 100,000 patients. Although prostate cancer was diagnosed more often in the intervention group (4.3% compared to 3.6% in the control group), the mortality rate was almost identical between both groups (Martin et al., 2018).

A systematic review and meta-analysis of 341,342 patients evaluated the overall effectiveness of prostate cancer screening. Results from this study showed that while PSA screening did lead to an increase in the identification of prostate cancer cases at all stages, it did not necessarily reduce the amount of overall or disease specific mortality rates (Ilic et al., 2018). This highlights the uncertainty regarding the effectiveness of prostate cancer screening. The authors also noted that "PSA screening is associated with considerable biopsy-related and cancer treatment-related complications" (Ilic et al., 2018).

In May of 2012, the USPSTF released a grade D recommendation against PSA prostate cancer screening (Ahlering et al., 2019). In 2018, the recommendation was switched to a grade C recommendation, now suggesting that men ages 55 to 69 could be screened for prostate cancer if first counseled about the benefits and harms of screening (USPSTF, 2018). Nonetheless, when the grade D recommendation was first released, many researchers were worried that an increase in late-stage prostate cancer cases would be identified, leading to greater rates of prostate cancer-specific mortality. To assess this risk, data from a total of 19,602 patients from nine high volume referral centers in the United States was collected and analyzed during the time that

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the USPSTF grade D recommendation was in effect. The researchers found that “All centers experienced consistent decreases of low-grade disease and absolute increases in intermediate and high-risk cancer. For any given age and PSA, propensity matching demonstrates more aggressive disease in the post-recommendation era” (Ahlering et al., 2019).

Osses, et al., (2019) assessed the results of 1,134 men screened for prostate cancer in a 19 year follow up study; at the start of the study, all men were between the ages of 55 and 74. Unfortunately, 63% of the cohort was deceased by the 19-year follow-up period for various reasons. Still, the researchers noted that results suggested “a more substantial reduction in metastatic disease and cancer-specific mortality in favor of prostate cancer screening than previously reported (Osses et al., 2019).” However, more research needs to be completed with a larger sample size to confirm this conclusion.

Magnani et al. (2021) performed a cost analysis on “first-line prostate cancer management” using real-world data. A total of 3433 patients were included, and outcomes such as active surveillance (AS), surgery, and radiation were considered. Surgery was found to be the most common option, with 54.6% of the cohort compared to 22.3% for radiation and 23% for AS. Over a period of 2 years following diagnosis, AS was found to be the cheapest option at \$2.97/day (d), with surgery costing \$5.67/d and radiation costing \$9.34/d, for “favorable” disease. For “unfavorable” disease, surgery cost \$7.17/d and radiation cost \$16.34/d. Over a period of 5 years following diagnosis, AS was found to be cheaper than surgery, by an amount of \$2.71/d to \$2.87 for surgery and \$4.36 for favorable disease. For unfavorable disease, surgery remained cheaper than radiation, by an amount of \$4.15/d to \$10.32/d. The authors did remark that this information came from a single health care system and were based on benchmark Medicare estimates rather than actual payment exchanges (Magnani et al., 2021).

Baniak et al. (2020) compared the clinicopathologic and molecular characteristics of prostate cancer in 90 younger men (45 years or younger) to 200 men of typical screening age (60-65 years). The authors found that younger men tended to have lower PSA values, but a higher frequency of family history of prostate cancer. No significant differences were found in staging or pathological characteristics of core biopsy specimens between the two groups. The younger cohort was also found to have a higher frequency of “grade group 1 disease” at radical prostatectomy. Finally, no statistically significant differences were found regarding prostatic adenocarcinoma prostate specific recurrence/progression or death between the two cohorts (Baniak et al., 2020).

Guidelines and Recommendations

The American Association of Family Physicians (AAFP) recommends against use of PSA-based testing for prostate cancer screening. For men between 55 to 69 years of age who are considering prostate cancer screening, the physician should discuss the risks and benefits and engage in shared decision making before undergoing the screening process. In addition, the AAFP recommends against prostate cancer screening in men older than 70 (AAFP, 2018b).

The American Academy of Family Physicians (AAFP)

The AAFP, with Choosing Wisely, have published guidelines on prostate cancer. These guidelines state that screening may prevent mortality, but “Whether this potentially small benefit in mortality outweighs the potential harms is dependent on the values and preferences of individual men. Therefore, for men who express a desire for prostate cancer screening, it should only be performed following a discussion of the potential benefits and harms. Routine screening for prostate cancer should not be done. PSA-based prostate cancer screening should not be performed in men over 70 years of age” (AAFP, 2018a).

The United States Preventive Services Task Force (USPSTF) issued additional draft guidelines which recommend that clinicians inform men aged 55 to 69 years about the potential benefits and harms of PSA-based screening for prostate cancer, noting that the decision to be screened should be up to the patient. The USPSTF also states that screening offers a small potential benefit of reducing the chance of dying of prostate cancer. However, they note many men will be harmed due to false positives and its side effects such as overdiagnosis or other complications such as impotence. The USPSTF recommends discussion with a clinician before deciding to screen, ultimately giving this screening a “C” recommendation. Furthermore, the USPSTF recommends against PSA-based screening for prostate cancer in men over 70 (USPSTF, 2018) The

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CDC follows the USPSTF recommendations as well (CDC, 2022b).

The Memorial Sloan Kettering Cancer Center

The Memorial Sloan Kettering Cancer Center issued screening guidelines on prostate cancer based on the individual's age. Their guidelines are for men who are expected to live at least ten years. "Men ages 45 to 49 should have a baseline PSA test. If the PSA level is 3 ng / mL or higher, men should talk with their doctor about having a biopsy of the prostate. If the PSA level is between 1 and 3 ng / mL, men should see their doctor for another PSA test every two to four years. If the PSA level is less than 1 ng / mL, men should see their doctor for another PSA test between the ages of 51 and 55. Men ages 50 to 59 should have their PSA level checked. If the PSA level is 3 ng / mL or higher, men should talk with their doctor about having a biopsy of the prostate. If the PSA level is between 1 and 3 ng / mL, men should see their doctor for another PSA test every two to four years. If the PSA level is less than 1 ng / mL, men should see their doctor for another PSA test at age 60. Men ages 60 to 70 should have their PSA level checked. If the PSA level is 3 ng / mL or higher, men should talk with their doctor about having a biopsy of the prostate. If the PSA level is between 1 and 3 ng / mL, men should see their doctor for another PSA test every two to four years. If the PSA level is less than 1 ng / mL, no further screening is recommended. Men ages 71 to 75 should talk with their doctor about whether to have a PSA test. This decision should be based on past PSA levels and the health of the man. Prostate cancer screening is not recommended for men ages 76 or older. A high PSA level does not generally mean that a man should have a prostate biopsy" (Center, 2022).

The National Cancer Coalition Network (NCCN) also recommends that patients make informed decisions regarding enrollment in an early detection program. Factors such as personal history, previous testing, family history, and race should be considered for determination if an early detection protocol is implemented. The guidelines stated that most panel members favored informed testing starting at 45. The panel supports screening in men until 75, and then continuing screening only in very healthy patients with little or no comorbidity to detect the life threatening and aggressive cancers. However, widespread screening in this age group is not recommended (NCCN, 2023b). The NCCN also noted their concern about "the problems of overtreatment related to the increased frequency of diagnosis of prostate cancer from widespread use of PSA for early detection of screening" (NCCN, 2023a).

For initial testing, the NCCN recommends that "baseline PSA testing should be offered to healthy, well-informed men aged 45 to 75 years based on the results of RCTs" (NCCN, 2023b). The NCCN also recommends screening starting at 40 years for certain higher risk populations, such as those with "African ancestry," "suspicious family history," and germline mutations that increase risk of prostate cancer. Further, baseline testing may be ordered along with a DRE, and any elevated levels should be double checked with repeat testing.

The NCCN considers three categories for "early evaluation detection," men of average risk (45-75 years), men of increased risk (such as men with "African ancestry", "suspicious family history" and "germline mutations that increase the risk of prostate cancer" [such as BRCA]), and men above 75 years.

- For men aged 45 to 75 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. If PSA > 3 ng/ml (or if the DRE is "very suspicious"), a biopsy should be considered.
- For high-risk populations, the above decision tree is identical for men of increased risk; the only difference is that NCCN recommends starting these evaluations at 40 years for the high-risk populations. The NCCN also writes to "consider" screening these high-risk populations "annually" rather than the less frequent intervals discussed.
- For men over 75 years, repeat testing in select patients at 1 – 4-year intervals is recommended if the PSA is <4 ng/ml, the DRE is normal, and there are no other indications for biopsy. If PSA >4 ng/ml, a repeat PSA test is recommended, followed-by a transrectal ultrasound (TRUS) or transperineal-guided biopsy.
- Regarding biopsies, the NCCN writes that a repeat PSA or other biomarkers that "improve specificity of screening" may be considered for evaluation. A follow-up 6-12 months after the biopsy to test for PSA may also be performed. If a biopsy is negative for cancer, the panel "recommends repeat PSA and DRE testing at 6- to 24-month intervals with consideration of

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repeat biopsy results.” (NCCN, 2023b).

The NCCN also comments on several biomarkers’ ability to assess early detection of prostate cancer.

- “cPSA”, the alpha-1-antichymotrypsin complexed form of PSA, has been shown to provide information similar to the traditional free PSA to total PSA ratio. cPSA has been approved “as an aid in the detection of prostate cancer in men aged 50 or older in conjunction with DRE” but has not seen much clinical use as of time of writing.

The NCCN also includes recommendations for PSA testing in non-screening situations, such as monitoring. Regarding “patients initially treated with intent to cure”, the NCCN recommends testing serum PSA levels “every 6 to 12 months for the first 5 years and then annually.” The NCCN also notes that for men with “high” risk of recurrence, testing PSA every 3 months may be preferred. For patients with “castration-naïve disease on ADT [androgen deprivation therapy], PSA measurement may be done every 3-6 months (NCCN, 2023a).

The American Cancer Society (ACS) recommends that physicians provide patients with information on benefits, risks, and uncertainties of the PSA test, and state that screening not be done until such information is received. The ACS recommends that discussions (and screening) begin at age 50 for males of average risk, at age 45 for those at increased risk (such African-American men), and at age 40 for those at highest risk (those with more than one first degree relative with a history of early-onset prostate cancer (ACS, 2021). After this discussion, men who want to be screened should get the PSA screening and the digital rectal exam (DRE). Because prostate cancer is slow-growing, the ACS does not recommend PSA screening in any individual with a life expectancy of less than 10 years, regardless of age or family history. If the initial PSA test is in normal range, the ACS recommends different testing intervals based on the initial test. For patients with results less than 2.5 ng/mL, the screening interval should be 2 years. For patients with initial results is at or higher than 2.5 ng/mL, the screening interval should be annually (ACS, 2021).

The National Cancer Institute (NCI) has deemed the evidence insufficient to determine whether PSA-based screening reduces mortality of prostate cancer. The NCI states that although screening can detect cancer in its earlier stages, it is unclear that earlier detection (and treatment) changes the natural course of the disease. The NCI also states that there is significant harm in screening such as overdiagnosis and complications caused by the screenings (NCI, 2022b). Moreover, NCI states there is “solid evidence,” that current treatments such as radical prostatectomy and radiation therapy, result in “permanent side effects in many men” (NCI, 2022b).

The American College of Physicians (ACP) agrees with the informed decision-making requirement for PSA testing, and states that clinicians should not screen using the PSA test in patients who “do not express a clear preference for screening”. The ACP recommends that these discussions take place for men of average risk, ages 50 to 69 years. ACP recommends against screening with PSA for individuals under 50 or over 70, and those with a life expectancy of less than 10 (Qaseem, et al., 2013; Wilt et al., 2015).

The American Urological Association (AUA)

The AUA recommends against use of PSA screening in men under 40, and routine screening for average-risk men between ages 40 to 54 years. The AUA does recommend informed decision making for men ages 55 to 69 years. The AUA recommends against PSA screening in men 70 years of age and older, or in any man with a life expectancy less than 10 – 15 years, although they do acknowledge that some men in excellent health 70 years and older may benefit from screening. The AUA recommends an individualized screening program be developed for individuals less than 55 years old, who are at high risk, such as those with a positive family history and African Americans. The AUA notes that a routine screening interval of two or more years may be preferred, but also notes that screening intervals “can be individualized by a baseline PSA level” (Carter et al., 2013).

The European Society for Medical Oncology (ESMO)

The ESMO recommends against population-based screening for prostate cancer because the reduction in mortality does not offset the harms done, such as overdiagnosis and overtreatment. Early PSA testing should

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only be offered to men > 50 years, men > 45 years with a family history of prostate cancer, African Americans > 45 years, and *BRCA1/2* carriers who are > 40 years of age. Prostate cancer screening should not be performed in asymptomatic men with a life expectancy of less than ten years. ESMO also recommends against screening in asymptomatic men over 70 (Parker et al., 2020).

The American Association of Clinical Urologists Inc. (AACU)

The AACU recommends use of tissue-based molecular testing to assess risk stratification in prostate cancer treatment decision making. The AACU states pursuing germline testing when appropriate is encouraged and support any further research into these tests AACU (AACU, 2018).

The European Association of Urology (EAU), European Society for Radiotherapy and Oncology (ESTRO) and International Society of Geriatric Oncology (SIOG)

Joint guidelines on prostate cancer screening and early detection from the EAU, ESTRO and SIOG include the table below taken from Mottet et al. (2020).

Do not subject men to prostate-specific antigen (PSA) testing without counselling them on the potential risks and benefits.	Strong
Offer an individualised risk-adapted strategy for early detection to a well-informed man with a good performance status (PS) and a life-expectancy of at least ten to fifteen years.	Weak
Offer early PSA testing in well-informed men at elevated risk of having PCa: men > 50 years of age; men > 45 years of age and a family history of PCa; African-Americans > 45 years of age. Men carrying <i>BRCA2</i> mutations > 40 years of age	Strong
Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of two years for those initially at risk: men with a PSA level of > 1 ng/mL at 40 years of age; men with a PSA level of > 2 ng/mL at 60 years of age; Postpone follow-up to eight years in those not at risk.	Weak
Stop early diagnosis of PCa based on life expectancy and performance status; men who have a life-expectancy of < fifteen years are unlikely to benefit.	Strong

Additional guidelines for the risk-assessment of asymptomatic men from (Mottet et al., 2020) state:

Recommendation	Strength rating
To avoid unnecessary biopsies, offer further risk-assessment to asymptomatic men with a normal digital rectal examination (DRE) and a prostate-specific antigen (PSA) level	Strong

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between 2-10 ng/mL prior to performing a prostate biopsy. Use one of the following tools: risk-calculator; imaging; an additional serum or urine-based test (weak strength rating)	
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The guideline also notes the presence of newer biological markers, such as “TMPRSS2-ERG fusion, PCA3, or kallikreins as incorporated in the Phi or 4Kscore tests” but despite promising early results, the guideline considers these markers to have “too limited data to implement these markers into routine screening programmes” (Mottet et al., 2020).

In 2021, the EAU released updated guidelines on their position regarding prostate antigen testing, recommending a risk-adapted strategy for the early detection of prostate cancer and reaffirming the joint guidelines in the table above. They noted that an absence of regular and routine widespread PSA testing had led to “opportunistic” testing in several EU member states. In addition, the impact of COVID-19, particularly the redeployment of medical resources to fight COVID-19, as well as a move during COVID-19 to “deprioritize all oncology screening, including PSA testing,” was of strong concern. Their position concluded with the need to reverse current unfavorable trends to accurately diagnose advanced stage prostate cancer and save lives (Van Poppel et al., 2021).

State and Federal Regulations, as applicable

The FDA has approved several screening tests for prostate cancer beginning with a PSA immunoassay in 1986 (FDA, 2023).

On June 14, 2012, the FDA approved the Access® Hybritech® p2PSA assay created by Beckman Coulter, Inc. From the FDA website: “The Access® Hybritech® p2PSA assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of [-2] proPSA antigen, an isoform of free PSA, in human serum using the Access Immunoassay Systems. Access@ Hybritech® p2PSA is intended to be used in combination with Access® Hybritech® (total) PSA and Access@ Hybritech@ free PSA to calculate the Beckman Coulter Prostate Health Index (phi), an In Vitro Diagnostic Multivariate Index Assay (IVDMIA)” (FDA, 2012a).

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 84152, 84153, 84154, G0103

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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For Policy Titled: Prostate Cancer Screening

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Medical Director review 4/2020

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Policy Implementation/Update Information

For Policy Titled: Prostate Cancer Screening

- 1/1/2019 New policy developed. BCBSNC will provide coverage for prostate cancer screening when it is determined to be medically necessary and criteria are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)
- 6/11/19 Reviewed by Avalon 1st Quarter 2019 CAB. Under “When Covered” section: changed “men” to “individuals.” Under “When Not Covered” section: re-ordered and re-worded indications. Updated “gene expression analysis” general terminology to include “use of Prolaris, Oncotype DX, Promark or Decipher tumor-based molecular assays to guide management of prostate cancer as well as urine testing.” Added PLA codes 0005U and 0047U to Billing/Coding section. Medical Director review 5/2019. (lpr)
- 10/1/19 Reviewed by Avalon 2nd Quarter 2019 CAB. Policy statement revised to read: BCBSNC will provide coverage for prostate cancer screening when it is determined the medical criteria and guidelines noted below are met. Revised Description Section. Wording changed in the When Covered section. “Medically Necessary” changed to “Reimbursement is allowed...” Wording revised in the Not Covered section. “Investigational” changed to read “Reimbursement is not allowed...” Deleted coding grid. Policy Guidelines updated. References added. Policy noticed 10/1/2019 for effective date 12/2/2019. (an)
- 12/31/19 Specialty Matched Consultant Panel review 8/21/19. No change to policy statement. CPT code 81542 added to Billing/Coding section for effective date 1/1/2020. (lpr)
- 3/24/2020 CPT codes 81541, 81551 and PLA code 0005U removed from Billing/Coding section. (lpr)
- 5/12/20 Reviewed by Avalon 1st Quarter 2020 CAB. Medical Director review 4/2020. Added CPT codes 0005U and 81551 to Billing/Coding section. Switched the term “testing” to “screening” in the “When Covered” section. Added ExoDx prostate, Intelliscore, Select MDX, PCA3, KLK3, Confirm MDX, PPCA to “When Not Covered” section. Updated Policy Guidelines and References. (lpr)
- 9/8/20 Specialty Matched Consultant Advisory Panel review 8/19/2020. No changes to policy statement. (lpr)

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For Policy Titled: Prostate Specific Antigen (PSA) Testing

- 5/18/21 Reviewed by Avalon 1st Quarter 2021 CAB. Medical Director review 4/2021. Under “When Covered” section: revised and updated to include total PSA testing for average risk individuals aged 45-75 with African ancestry, germline mutations that increase risk for prostate cancer, suspicious family history. Updated Description and Policy Guidelines sections as well as References. Revised and updated Billing/Coding section. **Policy title changed from: Prostate Cancer Screening to: Prostate Specific Antigen (PSA) Testing.** (lpr)
- 9/7/21 Specialty Matched Consultant Advisory Panel review 8/18/2021. No change to policy statement. (lpr)
- 5/17/22 Reviewed by Avalon 1st Quarter 2022 CAB. Medical Director review 4/2022. Updated guidelines/recommendations and references. (lpr)
- 7/18/23 Reviewed by Avalon 1st Quarter 2023 CAB. Medical Director review 4/2023. Deleted related policies section. Updated policy guidelines and references. Re-ordered and edited “when covered” section for clarity. No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.