Geisinger

Geisinger Health Plan Policies and Procedure Manual

Policy: MPA G2008

Section: Medical Policy

Subject: Prostate Specific Antigen (PSA) Testing

Applicable Lines of Business

Commercial	**x**	**CHIP**	**x**
Medicare	**x**	**ACA**	**x**
Medicaid	**x**		

I. Policy: Prostate Specific Antigen (PSA) Testing

II. Purpose/Objective: To provide a policy of coverage regarding

III. Responsibility:

A. Medical Directors
B. Medical Management

IV. Required Definitions

1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

Commercial

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Medicare

Geisinger Gold Medicare Advantage HMO, PPO, and HMO D-SNP plans are offered by Geisinger Health Plan/Geisinger Indemnity Insurance Company, health plans with a Medicare contract. Continued enrollment in Geisinger Gold depends on contract renewal. Geisinger Health Plan/Geisinger Indemnity Insurance Company are part of Geisinger, an integrated health care delivery and coverage organization.

CHIP

Geisinger Health Plan Kids (GHP Kids) is a Children's Health Insurance Program (CHIP) offered by Geisinger Health Plan in conjunction with the Pennsylvania Department of Human Services (DHS). Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Medicaid

Geisinger Health Plan Family (GHP Family) is a Medical Assistance (Medicaid) insurance program offered by Geisinger Health Plan in conjunction with the Pennsylvania Department of Human Services (DHS). Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

V. Additional Definitions

Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
b. provided for the diagnosis, and the direct care and treatment of the Member's condition, illness disease or injury;
c. in accordance with current standards of good medical treatment practiced by the general medical community.
d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and
e. the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient.

Medicaid Business Segment
Medically Necessary — A service, item, procedure, or level of care that is necessary for the proper treatment or management of an illness, injury, or disability is one that:

- Will, or is reasonably expected to, prevent the onset of an illness, condition, injury or disability.
- Will, or is reasonably expected to, reduce or ameliorate the physical, mental or developmental effects of an illness, condition, injury or disability.
- Will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for Members of the same age.

Policy Description

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.[1]

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.

Related Policies

Policy Number	Policy Title
AHS-G2007	Prostate Biopsy Specimen Analysis

Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1) For average-risk individuals 45 years of age and older (see Note 1), screening for prostate cancer with the total prostate-specific antigen (PSA) test **MEETS COVERAGE CRITERIA**.

2) For individuals 40 years of age and older (see Note 1), annual screening for prostate cancer with the total PSA test **MEETS COVERAGE CRITERIA** 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 with previous total PSA results, repeat screening for prostate cancer with a total PSA test **MEETS COVERAGE CRITERIA** 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- to 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- to 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 (see Note 1) at 1- to 3- year intervals.

4) A percent free PSA **or** a follow-up in 6-12 months with total PSA **MEETS COVERAGE CRITERIA** 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 (see Note 1) with a total PSA ≥4 ng/ml or a very suspicious DRE.

5) For individuals thought to be at a higher risk despite at least one prior negative prostate biopsy, follow-up testing with percent free PSA **MEETS COVERAGE CRITERIA**.

6) Total PSA testing **MEETS COVERAGE CRITERIA** 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 prostate cancer therapy.
   e) For detecting disease recurrence.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

7) The following testing **DOES NOT MEET COVERAGE CRITERIA**:
   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.

NOTES:

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 testing in this population would substantially increase rates of overdetection and is not recommended."[2] Additionally, the term individuals in this policy apply to individuals who have a prostate or were born with a prostate.

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."[3]

Table of Terminology

Term	Definition
AACU	American Association of Clinical Urologists Inc.
AAFP	The American Association of Family Physicians
ACP	The American College of Physicians
ACS	The American Cancer Society
ADT	Androgen deprivation therapy
AMACR	Alpha-methylacyl coenzyme a racemase
AS	Active surveillance
AUA	American Urological Association
BPH	Benign prostatic hyperplasia
BRCA	*Breast cancer gene, 1/2 mutation* (refers to *breast cancer gene 1* and *breast cancer gene 2*)
CCO	Cancer Care Ontario
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
CTFPHC	The Canadian Task Force on Preventive Healthcare
CUA	Canadian Urological Association
DRE	Digital rectal examination
EANM	European Association of Nuclear Medicine
EAU	European Association of Urology
ED	Erectile dysfunction
ESTRO	European Society for Radiotherapy and Oncology
ESUR	European Society of Urogenital Radiology
IVDMIA	In vitro diagnostic multivariate index assay
LDTs	Laboratory-developed tests
LUGPA	The Large Urology Group Practice Association
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
nmCRPC	Non-metastatic castration-resistant prostate cancer
NSAIDs	Non-steroidal anti-inflammatory drugs
PCA3	*Prostate cancer gene 3*
PHI	Prostate health index
PSA	Prostate-specific antigen
SIOG	International Society of Geriatric Oncology
SUO	Society of Urologic Oncology
TRUS	Transrectal ultrasound
USPSTF	The United States Preventive Services Task Force

Scientific Background

Prostate cancer is the most common cancer in American men (other than skin cancer) and the second leading cause of cancer death.[3] According to the CDC (2023), more than 236,000 prostate cancer cases are reported annually in the United States, leading to more than 33,000 prostate cancer deaths each year in 2022. The American Cancer Society estimates over 299,000 new cases and 35,000 deaths of prostate cancer in 2024.[5] Prostate cancer survival is related to many factors, especially the extent of the tumor at the time of diagnosis. The five year survival rate for men with localized or regional prostate cancer is nearly 100%, while the five 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 34%.[6,7] About one man in eight will be diagnosed with prostate cancer during his lifetime in the United States.[5]

Many cases of prostate cancer do not become clinically evident, as indicated in autopsy studies, where prostate cancer is detected in approximately 30% of men aged 55 or older and approximately 60% of men by age 80.[8] These data suggest that prostate cancer often grows so slowly that most men die of other causes before the disease becomes clinically advanced.[7]

Most prostate cancers use androgen-dependent signaling for development and progression.[9] 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.[10]

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.[11] Further, PSA levels tend to increase with age, suggesting that age-specific PSA reference ranges may be important for clinical use.[11]

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 identified but cannot be detected by commercial immunoassays and represents less than 0.1% of PSA.[12] Finally, unbound or free PSA, which is the enzymatically inactive form, can be found in 5-50% of serum samples.[12] Total PSA measures the amount of all PSA identified in a sample. Some researchers claim that the amount of total versus free PSA in a sample can foreshadow prostate cancer risk.[12] 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

Prostate-specific antigen (PSA) was originally introduced as a tumor marker to detect cancer recurrence or disease progression following treatment.[14] 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.[15] 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.[16]

As PSA is not a cancer-specific marker, it causes many false results that conflict with other screening methods, such as the digital rectal examination (DRE).[17] 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. 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 were <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.[18] 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.[1,18] Other factors such as medication can also affect PSA levels. Common medications, including statins, NSAIDs, acetaminophen, 5-alpha-reductase inhibitors, and thiazides, were all found to reduce PSA levels by varying degrees.[19-22]

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 1,000 individuals 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.[23]

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.[16] 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."[16]

In May of 2012, the USPSTF released a grade D recommendation against PSA prostate cancer screening.[24] 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.[25] 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 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."[24]

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."[26] 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 two 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 five 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.[27]

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 specific recurrence/progression or death between the two cohorts.[28]

Guidelines and Recommendations

The American Association of Family Physicians (AAFP)

The AAFP recommends against the 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.[29] They clarify that for men aged 55 to 69 "The decision to be screened for prostate cancer should be an individual one (Grade: C)," not to screen for prostate cancer in men aged 70 years and older (Grade: D). However, they also note that "older age, African American race, and family history of prostate cancer are the most important risk factors for prostate cancer." The workup they describe involve starting with a test to measure PSA in the blood, and then positive results may be followed up with a transrectal ultrasound-guided core-needle biopsy of the prostate to diagnose prostate cancer.[30]

The United States Preventive Services Task Force (USPSTF)

The USPSTF issued additional draft guidelines which recommend that clinicians inform men ages 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, many men may be harmed due to false positives and its side effects such as overdiagnosis or other complications such as impotence and urinary incontinence. 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.[25] The CDC cites the USPSTF recommendation.[31]

The Memorial Sloan Kettering Cancer Center (MSK)

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.

For ages 45 to 49:

- Consider benefits and risks of a baseline PSA level check:
  - If the baseline test is given, and the PSA level is 3 ng/mL or higher, consider a repeat PSA. If that PSA is still above 3 ng/mL, a secondary test, imaging, or biomarker test may be considered (to confirm or deny the need for prostate biopsy).
  - If the baseline test is between 1 and 3 ng/mL, consider another PSA test in two to four years. Two years is appropriate if the PSA is closer to three, and four years is appropriate if PSA is closer to one.
  - If the baseline test is less than 1 ng/mL, consider another PSA test between the ages of 51 and 55.

For ages 50 to 59:

- Consider benefits and risks of a baseline PSA level check:
  - If the baseline test is given and the PSA level is 3 ng/mL or higher, consider a repeat PSA. If that PSA

is still above 3 ng/mL, a secondary test, imaging, or biomarker test may be considered (to confirm or deny the need for prostate biopsy).
    - If the baseline test is between 1 and 3 ng/mL, consider another PSA test in two to four years. Two years is appropriate if the PSA is closer to three, and four years is appropriate if PSA is closer to one.
    - If the baseline test is less than 1 ng/mL, consider another PSA test at age 60.

For ages 60 to 70:

- Consider benefits and risks of a baseline PSA level check:
    - If the baseline test is given and the PSA level is 3 ng/mL or higher, consider a repeat PSA. If that PSA is still above 3 ng/mL, a secondary test, imaging, or biomarker test may be considered (to confirm or deny the need for prostate biopsy).
    - If the baseline test is between 1 and 3 ng/mL, consider another PSA test in two to four years. Two years is appropriate if the PSA is closer to three, and four years is appropriate if PSA is closer to one.
    - If the baseline test is less than 1 ng/mL, no more screening is recommended.

For ages 71 to 75:

- Individuals should discuss with a healthcare provider whether or not to perform a PSA test. The decision should be based on prior PSA levels and individual health background. Only consider repeat testing if PSA is high and health is overall good.

For ages 76 and older:

- Individuals should discuss with a healthcare provider whether to perform a PSA test. "In this age group, a PSA test is very rarely helpful."[32]

The National Comprehensive Cancer Network (NCCN)

The 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 and when 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 as it would increase rates of overdetection.[2] The NCCN also relayed 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."[33]

For initial testing, the NCCN recommends that "baseline PSA testing should be offered to healthy, well-informed individuals deemed to be at average risk aged 45 to 75 years based on the results of RCTs."[2] They also recommend 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 for prostate cancer. Further, baseline testing may be ordered along with a DRE, and any elevated levels should be double checked with repeat testing.[2]

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 for prostate cancer" [such as BRCA]), and men above 75 years.

- For men aged 45 to 75 years with average risk, the panel recommends repeat testing every 2 to 4 years if PSA is <1 ng/mL. If the PSA level is 1 to 3 ng/mL, frequency of testing should be every 1 to 2 years. If PSA > 3 ng/ml (or if the DRE is "very suspicious"), a biopsy should be considered.
- The above decision tree also applies to high-risk populations (African ancestry, suspicious or concerning family history, germline mutations that increase the rate of prostate cancer), though the NCCN recommends starting these evaluations at 40 years rather than 45 years of age. The NCCN also writes to "consider" screening these high-risk populations "annually" rather than the less frequent intervals discussed.

- For select patients over 75 years, repeat testing in select patients at 1- to 3-year intervals is recommended if the PSA is <4 ng/ml, the DRE is normal, and there are no other indications for biopsy. In this case, they also state that one should "Consider discontinuing screening if clinically appropriate."
- However, in select patients over 75 years of age, if the patient has PSA >4 ng/ml and/or a very suspicious DRE, a repeat PSA test, DRE (if not performed during initial risk assessment), and workup for benign disease is indicated. A multiparametric MRI (mpMRI) should be considered. However, it is noted that "A negative MRI does not exclude the possibility of cancer," and so it is recommended to "Consider biomarkers and/or PSA density when deciding whether to avoid a biopsy in an individual with a negative mpMRI result."
    - If there is high suspicion for clinically significant cancer, image-guided biopsy via transrectal or transperineal approach with MRI targeting or without MRI targeting is indicated, though MRI targeting is preferred
    - If there is low suspicion for clinically significant cancer, there should be a follow-up in 6-12 months with PSA/DRE.[2]

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

They note that "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", explaining that "Most immunoreactive PSA is bound to the protease inhibitor alpha-1-antichymotrypsin. Other immunoreactive PSA-protease inhibitor complexes, such as alpha-1-antitrypsin and protease C inhibitor, exist at such low serum concentrations that their clinical significance has not been determined."[2] Another notable proportion of PSA is complexed with alpha-2-macroglobulin (AMG), though "this PSA-AMG complex cannot be measured by conventional assays because of the shielding (or "caging") of PSA antigenic epitopes by AMG."[2]

Testing for %fPSA is included in the NCCN guidelines as "an option before initial biopsy and for those with a prior negative biopsy" since "the FDA approved the use of %fPSA for the early detection of prostate cancer in individuals aged ≥50 years with a non-suspicious DRE and PSA levels between 4 ng/mL and 10 ng/mL (PSA levels where most secondary testing is done). The multi-institutional study that characterized the clinical utility of this assay showed that a 25% fPSA cutoff detected 95% of prostate cancers while avoiding 20% of unnecessary prostate biopsies."[2]

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 three months may be preferred. For patients with castration-naïve disease on ADT [androgen deprivation therapy], PSA measurement may be done every three to six months based on clinical judgement. Moreover, the NCCN notes that "Local recurrence may result in substantial morbidity and can, in rare cases, occur in the absence of a PSA elevation. Therefore, annual DRE is appropriate to monitor for prostate cancer recurrence and to detect colorectal cancer. Similarly, after RT, the monitoring of serum PSA levels is recommended every six months for the first five years and then annually and a DRE is recommended annually. The clinician may opt to omit the DRE if PSA levels remain undetectable."[33]

The American Cancer Society (ACS)

The 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 individuals of average risk, at age 45 for those at increased risk (i.e., "African American men and men who have a first-degree relative (father or brother) diagnosed with prostate cancer at an early age (younger than age 65)"), 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).[34]

After having this discussion, individuals who want to be screened should get the PSA screening. A DRE may also be performed. Because prostate cancer grows slowly, the ACS does not recommend PSA screening in any individual without symptoms of prostate cancer and with a life expectancy of less than 10 years. However, they also note that overall health and not age alone is important to decide when to pursue screening.[34]

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 at or higher than 2.5 ng/mL, the screening interval should be annually.[34]

The ACS remarks that overall health and not age alone is important to decide when to pursue screening. Moreover, "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" and further discussions must incorporate patients' health, values, and preferences.[34]

The National Cancer Institute (NCI)

The NCI has deemed the evidence insufficient to determine whether PSA-based screenings or DREs reduce mortality from 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.[35] 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."[35]

The American College of Physicians (ACP)

The 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. It is also worth mentioning that "it has been suggested that those who are at high-risk may benefit from earlier screening beginning at age 45, while even higher risk men (those with two or more first-degree relatives with prostate cancer before age 65) should be screened at age 40." The ACP recommends against screening with PSA for individuals under 50 or over 70, as the primary target is between the ages of 50 and 69. The ACP also cautions that "Clinicians should not screen for prostate cancer using the PSA test in average-risk men aged 50 to 69 years who have not had an informed discussion and do not express a clear preference for screening."[36] Asymptomatic men over 75 and those with a life expectancy of less than 10 years should also not be offered screening because screening can introduce substantial harms for questionable benefit.[36,37]

The American Urological Association (AUA) and the Society of Urologic Oncology (SUO)

The AUA and the SUO collaborated to produce a series of guideline statements. Regarding the use of PSA screening in the early detection of prostate cancer, they expounded that:

- "1. Clinicians should engage in SDM with people for whom prostate cancer screening would be appropriate and proceed based on a person's values and preferences. (*Clinical Principle*)"
- "2. When screening for prostate cancer, clinicians should use PSA as the first screening test. (*Strong Recommendation; Evidence Level: Grade A*)"
- "3. For people with a newly elevated PSA, clinicians should repeat the PSA prior to a secondary biomarker, imaging, or biopsy. (*Expert Opinion*)"
- "4. Clinicians may begin prostate cancer screening and offer a baseline PSA test to people between ages 45 to 50 years. (*Conditional Recommendation; Evidence Level: Grade B*)"
- "5. Clinicians should offer prostate cancer screening beginning at age 40 to 45 years for people at increased risk of developing prostate cancer based on the following factors: Black ancestry, germline mutations, strong family history of prostate cancer. (*Strong Recommendation; Evidence Level: Grade B*)"
- "6. Clinicians should offer regular prostate cancer screening every 2 to 4 years to people aged 50 to 69

years. (*Strong Recommendation; Evidence Level: Grade A*)"

- "7. Clinicians may personalize the re-screening interval, or decide to discontinue screening, based on patient preference, age, PSA, prostate cancer risk, life expectancy, and general health following SDM. (*Conditional Recommendation; Evidence Level: Grade B*)"
- "8. Clinicians may use digital rectal exam (DRE) alongside PSA to establish risk of clinically significant prostate cancer. (*Conditional Recommendation; Evidence Level: Grade C*)"
- "9. For people undergoing prostate cancer screening, clinicians should not use PSA velocity as the sole indication for a secondary biomarker, imaging, or biopsy. (*Strong Recommendation; Evidence Level: Grade B*)"
- "10. Clinicians and patients may use validated risk calculators to inform the SDM process regarding prostate biopsy. (*Conditional Recommendation; Evidence Level: Grade B*)"
- "11. When the risk of clinically significant prostate cancer is sufficiently low based on available clinical, laboratory, and imaging data, clinicians and patients may forgo near-term prostate biopsy. (*Clinical Principle*)."[38]

The AUA and SUO also partnered to discuss advanced prostate cancer as well, reported below.[39]

Regarding the use of PSA screening for the Biochemical Recurrence without metastatic disease after Exhaustion of Local Treatment Options, they proposed that "Clinicians should inform patients with PSA recurrence after exhaustion of local therapy regarding the risk of developing metastatic disease and follow such patients with serial PSA measurements and clinical evaluation. Clinicians may consider radiographic assessments based on overall PSA and PSA kinetics. *(Clinical Principle).*"

Moreover, PSA screening also plays a role in the prognosis of Metastatic Hormone-Sensitive Prostate Cancer, such that "Clinicians should obtain a baseline PSA and serial PSAs at three- to six-month intervals after initiation of ADT in mHSPC patients and consider periodic conventional imaging. *(Clinical Principle).*"

In patients with Non-Metastatic Castration-Resistant Prostate Cancer (nmCRPC), "clinicians should obtain serial PSA measurements at three- to six-month intervals, and calculate a PSADT starting at the time of development of castration-resistance. *(Clinical Principle).*"

Lastly, in patients with Metastatic Castration-Resistant Prostate Cancer, "clinicians should obtain baseline labs (e.g., PSA, testosterone, LDH, Hgb, alkaline phosphatase level) and review location of metastatic disease (lymph node, bone, visceral), disease-related symptoms, and performance status to inform discussions of prognosis and treatment decision-making. *(Clinical Principle).*" However, "In mCRPC patients without PSA progression or new symptoms, clinicians should perform imaging at least annually. *(Expert Opinion).*"[39]

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 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.[40]

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 pursing germline testing when appropriate is encouraged and support any further research into these tests.[41]

The European Association of Urology (EAU)

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 "deprioritise all oncology screening, including PSA testing," was of strong concern. Their position concluded with the need to reverse current unfavorable trends in order to accurately diagnose advanced stage prostate cancer and save lives.[42]

The European Association of Urology (EAU), European Association of Nuclear Medicine (EANM), European Society for Radiotherapy and Oncology (ESTRO), European Society of Urogenital Radiology (ESUR), and International Society of Geriatric Oncology (SIOG)

Joint guidelines on prostate cancer screening and early detection from the EAU, EANM, ESTRO, ESUR, and SIOG include the table below taken from Cornford, et al. (2024):

Recommendation	Strength Rating
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 life-expectancy of at least 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;** **men of African descent > 45 years of age;** **men carrying *BRCA2* 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 Cornford, et al. (2024) state:

Recommendation	Strength rating
In asymptomatic men with a prostate-specific antigen (PSA) level between 3 and 10 ng/mL and a normal digital rectal examination (DRE), repeat the PSA test prior to further investigations.	Weak

The guideline also notes the presence of newer biological markers, "the use of biomarkers (included in a nomogram) may help in predicting indolent PCa. Several assays measuring a panel of kallikreins in serum or plasma are now commercially available..." However, regarding urine and blood-based biomarker tests, "further studies are necessary to validate their efficacy."[43]

Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration

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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

The FDA has approved several screening tests for prostate cancer beginning with a PSA immunoassay in 1986.[44]

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)."[45]

Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
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)

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

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Revision History

Effective Date	Summary
07/01/2025	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria:

	CC1 and CC2, replaced "-75" with "and older (see Note 1)", as testing is allowed 45+ (CC1) or 40+ (CC1) at the frequencies in CC4. Results in removal of CC3. Former CC4.c., and CC5.b., now CC3.c. and CC4.b., edited for clarity, replaced mention of "little to no comorbidities" with "(see Note 1)" Former CC4.c., now CC3.c., updated interval from "1- to 4-year" to "1- to 3-year"
06/01/2024	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following edits were made for clarity: Removed TRUS-guided biopsy and DRE from CC5, as these are outside Avalon's scope of management. CC 5 now reads: "5) A percent free PSA test or a follow-up in 6-12 months with total PSA MEETS COVERAGE CRITERIA when any of the following conditions are met:" Addition of "prostate cancer" to CC7.d. for clarity. Now reads: "d) For monitoring response to prostate cancer therapy."
07/15/2023	Annual Review: Literature review did not necessitate changes to coverage criteria. Policy edited for clarity and consistency.
06/01/2022	Initial Policy Implementation

Medicaid Business Segment:
Any requests for services, that do not meet criteria set in the PARP, may be evaluated on a case by case basis.

LINE OF BUSINESS:
Eligibility and contract specific benefits, limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supersede this policy. For Medicare, applicable LCD's and NCD's will supercede this policy. For PA Medicaid Business segment, this policy applies as written.