Prostate Specific Antigen (PSA) Testing

Policy Number: AHS – G2008 – Prostate Specific Antigen (PSA) Testing	Prior Policy Name and Number, as applicable: G2008 – Prostate Cancer Screening
Initial Presentation Date: 06/01/2021 Revision Date: N/A	

I. 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 (Freedland, 2020).

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

II. Related Policies

Policy Number	Policy Title
AHS-G2007	Prostate Biopsies
AHS-G2009	Preventive Screening in Adults
AHS-M2166	Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Medical Policy Statements do not ensure an authorization or payment of services. Please refer to the plan contract (often referred to as the Evidence of Coverage) for the service(s) referenced in the Medical Policy Statement. If there is a conflict between the Medical Policy Statement and the plan contract (i.e., Evidence of Coverage), then the plan contract (i.e., Evidence of Coverage) will be the controlling document used to make the determination.

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. If there is a conflict between this Policy and any relevant, applicable government policy [e.g. National Coverage

Determinations (NCDs) for Medicare] for a particular member, then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

1. Screening for prostate cancer with the total prostate-specific antigen (PSA) test MEETS COVERAGE CRITERIA for average-risk individuals aged 45-75 years.
2. Screening for prostate cancer with the total prostate-specific antigen (PSA) test annually MEETS COVERAGE CRITERIA for individuals aged 40-75 years with: a. African ancestry
   b. Germline mutations that increase risk for prostate cancer
   c. Suspicious family history
3. For individuals over 75 years, screening for prostate cancer with a total PSA test MEETS COVERAGE CRITERIA only for individuals with little or no comorbidities. (*See Note 1 below)
4. Repeat screening for prostate cancer with a total PSA test MEETS COVERAGE CRITERIA for individuals with previous total PSA results with the following frequency:
   a. For individuals aged <75 years, total PSA <1 ng/ml and DRE normal (if done): Repeat screening at 2-4 year intervals
   b. For individuals aged <75 years, total PSA 1-3 ng/ml and DRE normal (if done): Repeat screening at 1-2 year intervals
   c. For individuals aged <75 years, total PSA >3 ng/ml and/or very suspicious DRE: Any one of the following MEETS COVERAGE CRITERIA
      i. TRUS-guided biopsy ii. Follow-up in 6-12 months with total PSA or DRE iii. Percent free PSA
   d. For individuals aged >75 years, total PSA <4 ng/ml and DRE 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
   e. For individuals aged >75 years, total PSA ≥4 ng/ml or very suspicious DRE: Any one of the following MEETS COVERAGE CRITERIA in select patients (very healthy individuals with little or no comorbidity):

i. TRUS-guided biopsy ii. Follow-up in 6-12 months

with total PSA or DRE iii. Percent free

PSA

5. Follow-up testing with percent free PSA MEETS COVERAGE CRITERIA in patients thought to be at a higher risk despite at least one prior negative prostate biopsy.

6. Total PSA testing MEETS COVERAGE CRITERIA for initial prostate cancer diagnosis in individuals with signs and symptoms of prostate cancer (See Note 2), for follow-up of individuals with a current or previous diagnosis of prostate cancer, for ongoing monitoring of individuals who have undergone tumor resection or prostatectomy, for monitoring response to therapy, and 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 a patient's illness.

7. Testing in the following situations DOES NOT MEET COVERAGE CRITERIA:

   a. Use of percent free PSA as a first-line screening test for prostate cancer

   b. Routine prostate cancer screening using percent free PSA, free-to-total PSA ratio, and complexed PSA tests.

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 overdetection and is not recommended (NCCN, 2021)." 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 (ACS, 2019)."

IV. Scientific Background

Prostate cancer is the most common cancer in American men and the second leading cause of death in men over 65 (Balducci, Pow-Sang, Friedland, & Diaz, 1997; Tabayoyong & Abouassaly, 2015). According to the CDC (2016, 2017), more than 207,000 prostate cancer cases are reported annually in the United States, leading to more than 30,000 prostate cancer deaths each year. The American Cancer Society estimates over 191,000 new cases and 33,000 deaths of prostate cancer in 2020 (American_Cancer_Society, 2020). Prostate cancer survival is related to many factors, especially the extent of the tumor at the time of diagnosis. The 5-year survival rate 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 30% (ACS, 2019; Hoffman, 2020). About one man in nine will be diagnosed with prostate cancer during his lifetime in the United States (American_Cancer_Society, 2020).

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 age 55 or older and approximately 60 percent of men by age 80 (K. J. Bell, Del Mar, Wright, Dickinson, & Glasziou, 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, 2020).

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, Butler, Estelles, & de Bono, 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, 2017). Further, PSA levels tend to increase with age, suggesting that age-specific PSA reference ranges may be important for clinical use (NCI, 2017).

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 (Prcic, Begic, & Hiros, 2016). Finally, unbound or free PSA, which is the enzymatically inactive form, can be found in 5-50% of serum samples (Prcic et al., 2016). 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 (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 (Hoffman, 2020). It has become 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, Carlsson, & Roobol, 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).

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) (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. 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 (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, 2020; Stimac et al., 2014). Other factors such as medication can also affect PSA levels. Common medications, including statins, NSAIDs, acetaminophen, 5-alphareductase inhibitors, and thiazides, were all found to reduce PSA levels by varying degrees (Chang, Harshman, & Presti, 2010; Hamilton, Goldberg, Platz, & Freedland, 2008; Singer, Palapattu, & van Wijngaarden, 2008; Wang, Liu, Kreis, & Budman, 1997).

Clinical 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 PSAbased screening (n = 219439) found no difference in cancer mortality after a median follow-up of 10 years. The mortality rate in 1000 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 (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 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 postrecommendation era (Ahlering et al., 2019)."

Osses, Remmers, Schroder, van der Kwast, and Roobol (2019) assessed the results of 1134 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 followup 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. 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. 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 (PCa)-specific recurrence/progression or death between the two cohorts (Baniak et al., 2020).

V. Guidelines and Recommendations

The American Association of Family Physicians (AAFP, 2018b)

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 (AAFP, 2018b).

The American Academy of Family Physicians (AAFP, 2018a)

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. PSAbased prostate cancer screening should not be performed in men over 70 years of age (AAFP, 2018a)."

The United States Preventive Services Task Force (USPSTF, 2018)

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. 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 CDC follows the USPSTF recommendations as well (CDC, 2020).

The National Cancer Coalition Network (NCCN, 2020b, 2021)

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 (NCCN, 2021). 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, 2020a).

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, 2021)." 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 highrisk 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 repeat biopsy results." (NCCN, 2021).

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

- "cPSA", the alpha-1-antichemotrypsin 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, 2020b).

The American Cancer Society (ACS, 2020)

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 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, 2020). 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, 2020).

The National Cancer Institute (NCI, 2020)

The 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, 2020).

The American College of Physicians (ACP) (Qaseem, Barry, Denberg, Owens, & Shekelle, 2013; Wilt, Harris, & Qaseem, 2015)

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. Finally, the ACP recommend against screening with PSA for individuals under 50 or over 70, and those with a life expectancy of less than 10 years (Qaseem et al., 2013; Wilt et al., 2015).

The American Urological Association (AUA) [(Carter et al., 2013) reaffirmed 2018]

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 it is acknowledged 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) (Parker et al., 2015, 2020b)

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 (Parker et al., 2020a, 2020b).

The American Association of Clinical Urologists Inc. (AACU, 2018)

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. The Large Urology Group Practice Association (LUGPA) endorses this position statement by the AACU (AACU, 2018; LUGPA, 2018).

The European Association of Urology (EAU), European Society for Radiotherapy and Oncology (ESTRO) and International Society of Geriatric Oncology (SIOG) (Mottet et al., 2020)

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 wellinformed 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 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 (Mottet et al., 2020) state:

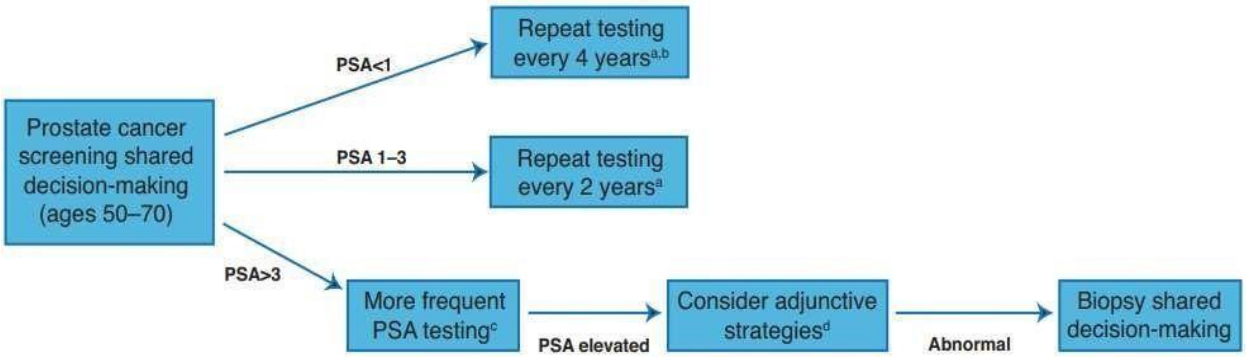
Recommendation	Strength rating
To avoid unnecessary biopsies, offer further risk-assessment to asymptomatic men with a normal digital rectal examination (DRE) and a prostate-specific antigen (PSA) level between 2-10 ng/mL prior to performing a prostate biopsy. Use one of the following tools: risk-calculator; imaging; an additional serum or urine-based test (weak strength rating)	Strong

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)

Canadian Urological Association (CUA) (Rendon et al., 2017)

In regards to PSA screening, the CUA recommends that prostate cancer screening be offered to men with a life expectancy of more than ten years, and that screening should only commence after all benefits and harms are discussed (Rendon et al., 2017). For all men who wish to undergo PSA screening, testing should begin at age 50, or age 45 for men with an increased risk of prostate cancer.

For men who do elect PSA screening, the following chart was given by Rendon et al. (2017):



Cancer Care Ontario (CCO, 2017)

Guidelines from the CCO state that due to the potential harms of screening and over-diagnoses, the CCO "does not support an organized, population-based screening program for prostate cancer (CCO, 2017)." The CCO continues by stating that all screening should be decided on an individual basis with patients discussing the screening process with a primary care provider.

The Canadian Task Force on Preventive Healthcare (CTFPHC) (Bell et al., 2014)

The CTFPHC has published guidelines stating that for men of all ages, not previously diagnosed with cancer, PSA screening is not recommended. For men younger than 55 years and older than 70 years, this is a strong recommendation, and for men aged 55-69 years, this is a weak recommendation (Bell et al., 2014).

VI. State and Federal Regulations, as applicable

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

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, 2012).

A search of the FDA database on 12/28/2020 using the term "PSA" yielded 97 results. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratorydeveloped tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as highcomplexity 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.

VII. Applicable CPT/HCPCS Procedure Codes

Code Number	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.

VIII. Evidence-based Scientific References

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IX. Revision History

Revision Date	Summary of Changes
06/01/2021	Initial presentation