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Corporate Medical Policy

Prostate Cancer Screening AHS - G2008

File Name:	prostate_cancer_screening
Origination:	1/1/2019
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Description of Procedure or Service

Prostate cancer is characterized by malignancy which originates in the small walnut-shaped gland in men that produces the seminal fluid. Heterogeneous in both molecular alterations and clinical course (Benedettini, Nguyen, & Loda, 2008), clinical course ranges from a microscopic tumor that never becomes clinically significant to aggressive disease that ultimately causes metastases, morbidity, and death (Kantoff, Tapli, & Smith, 2018).

Related Policies:
Prostate Biopsies AHS-G2007
Preventative Screening in Adults AHS-G2009
Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management AHS-M2166

******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 cancer screening 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 Cancer Screening is covered

1. Reimbursement is allowed for screening for prostate cancer with the prostate-specific antigen (PSA) test for all individuals aged 45-75 years. For individuals over 75 years, reimbursement is allowed for screening with a PSA test only for very healthy individuals with little or no comorbidities. (*See Note 1 below)
2. Reimbursement is allowed for repeat screening for prostate cancer for individuals with previous PSA results with the following frequency:
   A. For individuals aged 45-75 years, PSA <1 ng/ml and DRE normal (if done): Repeat screening at 2-4 year intervals
   B. For individuals aged 45-75 years, PSA 1-3 ng/ml and DRE normal (if done): Repeat screening at 1-2 year intervals

C. For individuals aged 45-75 years, PSA >3 ng/ml or very suspicious DRE: reimbursement is allowed for any one of the following**:**

   a. TRUS-guided biopsy

   b. Follow-up in 6-12 months with PSA or DRE

   c. Percent free PSA

D. For individuals aged >75 years, PSA <4 ng/ml and DRE normal (if done) and no other indications for biopsy: Reimbursement is allowed for repeat testing in select patients (very healthy individuals with little or no comorbidity) at 1-4 year intervals

E. For individuals aged >75 years, PSA ≥4 ng/ml or very suspicious DRE: reimbursement is allowed for any one of the following in select patients (very healthy individuals with little or no comorbidity):

   a. TRUS-guided biopsy

   b. Follow-up in 6-12 months with PSA or DRE

   c. Percent free PSA

3. Reimbursement is allowed for follow-up testing with percent free PSA in patients thought to be at a higher risk despite at least one prior negative prostate biopsy
4. Reimbursement is allowed for PSA testing annually for individuals with signs or symptoms of prostate cancer or in high-risk populations (eg African-American individuals and individuals with a family history of prostate cancer or men with a presence of inherited mutations).
5. Reimbursement is allowed for PSA testing for follow-up of individuals with a current or previous diagnosis of prostate cancer, and for ongoing monitoring of individuals who have undergone tumor resection or prostatectomy.

* NOTE 1: According to the NCCN guidelines, "Testing after 75 years of age should be done only in very healthy individuals with little or no comorbidity (especially if they have never undergone PSA testing) 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, 2018b, 2019a)." Additionally, the term individuals in this policy apply to individuals who have a prostate or were born with a prostate.

When Prostate Cancer Screening is not covered

Reimbursement is not allowed for:

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,

C. Other screening tests for prostate cancer that are not listed in the when covered section, including, but not limited to, alpha-methylacyl coenzyme A racemase (AMACR).

D. Tests using cellular and biologic features of a tumor, including use in predicting risk of recurrence in patients with prostate cancer,

Testing in the following situations is considered **investigational:**

A. Early prostate cancer antigen, endoglin, E twenty-six (ETS) gene fusions, human kallikrein 2, analysis of prostatic fluid electrolyte composition, interleukin-6, transforming growth factor-beta 1, TMPRSS2:ERG gene fusion.

B. Gene hypermethylation testing (ConfirmMDX).

C. Urine testing for gene expression profile and/or protein biomarkers, including ExoDx Prostate (Intelliscore) and SelectMDx.

D. Prostate cancer gene 3 (PCA3) testing.

E. PCA3/KLK3 (prostate cancer antigen 3/kallikrein-related peptidase 3 ratio.

F. Proveri Prostate Cancer Assay (PPCA).

G. Use of 4Kscore, Prostate Health Index (PHI), PCA3 score.

Policy Guidelines

Prostate cancer (PCa) 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), more than 190,000 prostate cancer cases are reported annually in the United States, leading to more than 30,000 prostate cancer deaths each year. Similar statistics are expected from 2019 (Smith et al., 2019). 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 30% (ACS, 2019; Hoffman, 2018). About one man in nine will be diagnosed with prostate cancer during his lifetime in the United States (Siegel, Miller, & Jemal, 2018).

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 (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, 2018).

Most prostate cancers use androgen-dependent signaling for development and progression (Fisher et al., 2015). As the number of targeted therapy agents increases, 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 PCa into different subtypes, yet the utility of this in the clinical setting is to be determined (Rodrigues, Butler, Estelles, & de Bono, 2014).

Pritchard et al found that the incidence of germline mutations in genes mediating DNA integrity (*BRCA2, ATM, CHEK2*, etc) among men with metastatic prostate cancer was 11.8%, which was significantly higher than the rate among men with localized prostate cancer. The frequency of germline mutations was evaluated at 4.6% among 499 men with localized prostate cancer and 2.7% of 53,105 individuals with any cancer diagnosis. Neither age nor family history affected the frequency of germline mutations (Pritchard et al., 2016).

Prostate-specific antigen (PSA) is the most widely accepted biomarker for prostate cancer screening. Prostate-specific antigen (PSA), a glycoprotein produced by prostate epithelial cells, was originally introduced as a tumor marker to detect cancer recurrence or disease progression following treatment (Hoffman, 2018). 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 lower quality of life (Fleshner, Carlsson, & Roobol, 2017).

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). 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. 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, 2017; 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, Harshman, & Presti, 2010; Hamilton, Goldberg, Platz, & Freedland, 2008; Singer, Palapattu, & van Wijngaarden, 2008; Wang, Liu, Kreis, & Budman, 1997).

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 person-years. 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).

Prolaris

The test "Prolaris" (created by Myriad Genetics) has been used to inform decision making on active surveillance (AS) and whether to proceed to a treatment option such as radiation or surgery. Prolaris is an assessment of the average expression of 31 cell-cycle progression (CCP) genes compared to 15 reference genes. This score is combined with the patient's age, PSA, percent positive cores, clinical stage, Gleason score, and AUA risk category and is intended to provide a 10-year prostate cancer-specific mortality risk. Scores range from 0 to 10, with each unit increase representing a doubling of disease risk progression. Prolaris may also be used to assess risk post-prostatectomy, and the same scale of 0-10 is used. Each unit increase represents a doubling of risk of biochemical recurrence (BCR) (Alford et al., 2017).

CCP expression has found to correlate with mortality rate of prostate cancer. Cuzick et al found that not only was there a relationship between CCP expression and mortality rate, the increased expression of CCP was predictive of BCR after 10 years. Even after adjusting for factors such as PSA and Gleason score, the CCP was both "highly significant" and "independent" of prostate cancer mortality rate. The authors noted that the CCP score could be created from minimal tumor mass (as little as 0.5 mm), with a 90% success rate with >0.5 mm visible tumor, as well as Prolaris' purely objective criteria compared to the Gleason score (Cuzick et al., 2015).

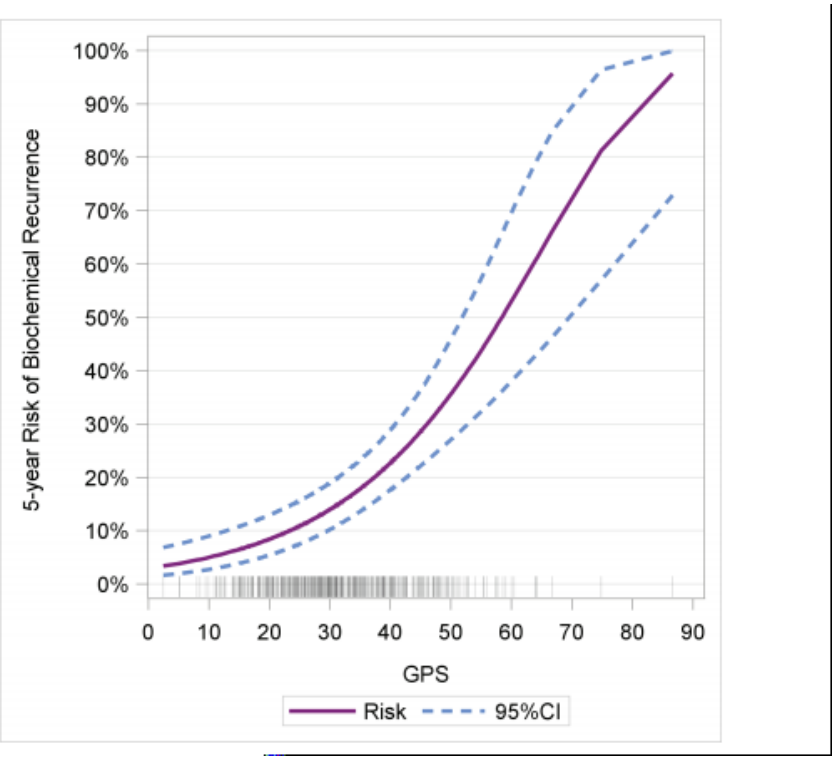
Prolaris may be used to lower unnecessary treatment by providing a molecular indication of the disease's progression. Radical treatments, such as prostatectomies, are often unnecessary, and there is utility in a biomarker metric than can reliably inform providers of a course of treatment or condition. An AS status is preferable to treatment. Hu et al. were able to use data provided by the CCP score (along with two other biomarker tests) to perform risk stratification and assess whether further treatment was needed or if the condition could be managed by active surveillance. Lin et al were able to clearly separate high and low risk patients using the CCP score. The study combined the CCP score as well as a clinical assessment from CAPRA into a cell-cycle risk (CCR) score. This CCR score was used to select patients for an AS status. The threshold created from both the molecular measures and the clinical measures has the advantage of including higher-risk patients whose clinical features may be lower-risk. Furthermore, the patients that fell below the threshold were found to have a mortality risk of 2.5%, and the probability of survival of patients with scores under the threshold was 100% (Hu et al., 2018; Lin et al., 2018). Finally, Prolaris has been used by providers to inform clinician decision making. A survey by Crawford et al found that the course of treatment for prostate cancer patients was influenced by Prolaris' results. About 65% of cases were reported to have shifted in the intended treatment based on the test results, and about 40% were reported to have opted for the AS choice (a "decrease" in treatment) (Carneiro et al., 2018).

Other biomarker tests exist as well. The NCCN specifically mentions Decipher, Oncotype DX and ProMark

as options to consider.

Oncotype DX

Oncotype DX is similar to Prolaris in that it assesses levels of gene expression, should be used for lower-risk patients, and used to inform clinicians about the course of treatment. The primary difference is that Oncotype DX only tests 12 genes, with 5 reference genes (compared to 31 and 15, respectively, for Prolaris). These expression levels are combined into an algorithm to produce a GPS score of 0-100. This GPS score correlated with prediction of cancer aggression (outcomes such as death or recurrence) (Cullen et al., 2015). Cullen et al. found that GPS score correlated with BCR as shown in the figure below:



Cullen then noted that OncoType DX was a good predictor of both early and late BCR and is validated for adverse pathology whereas Prolaris is validated for 10-year mortality or BCR after radical prostatectomy (Alford et al., 2017; Cullen et al., 2015; Davis, 2014; NCCN, 2018a).

Decipher

Decipher is a genomic and prognostic test that is used to predict cancer outcomes in patients that have undergone a radical prostatectomy (RP). It relies on the expression levels of 22 RNA markers in the RP specimen and is primarily used to predict likeliness of metastases or mortality. The algorithm score ranges from 0 to 1, where a higher score corresponds higher chance of metastasis. This algorithm was shown to have outperformed the traditional assessment of clinical and pathological features in predicting metastasis (0.75 accuracy compared to 0.69) as well as 17 other genetic tests (0.54 to 0.68 accuracy) (Alford et al., 2017; Dalela, Löppenberg, Sood, Sammon, & Abdollah, 2016).

ProMark

Another test that may have utility is ProMark. It measures the levels of eight proteins through quantitative immunofluorescence of a biopsy specimen. It is used to predict cancer aggression in patients with a Gleason score of 3+3 or 3+4. The proteins chosen have roles in cell proliferation, signaling, or stress response, and the score is reported from 1-100. This score represents individualized risk. Blume-Jensen et al narrowed down the 8 primary protein biomarkers used (down from the 12 proposed by an earlier study) as well as assessed its ability to predict clinical endpoints of favorable and nonfavorable disease. They recommended a cutoff of 0.33 (on a scale of 0-1) for “nonfavorable” pathology (83.6% of patients with favorable disease fell below

this cutoff). Conversely, a cutoff of 0.8 was recommended for favorable pathology as 76.9% of patients with nonfavorable pathology were above this cutoff. The authors concluded that this assay provided useful information, especially when differentiating between Gleason scores (Alford et al., 2017; Blume-Jensen et al., 2015).

Guidelines and Recommendations

The **American Association of Family Physicians (AAFP)** recommend against use of PSA-based testing for prostate cancer screening. In addition, the AAFP recommends that "Prostate cancer screening should not be performed in men older than 70. (AAFP, 2012).

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

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, 2018)."

The **United States Preventive Services Task Force (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, 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 CDC follows the USPSTF recommendations as well (CDC, 2018).

The National Cancer Coalition Network (NCCN) (NCCN, 2018a, 2018b, 2019a, 2019b)

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 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.

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, a repeat PSA test is recommended, followed-up with PSA testing in 6 to 12 months. For men over 75 years, repeat testing in select patients at 1-4 year intervals is recommended if the PSA is <4 ng/ml. If PSA >4 ng/ml, a repeat PSA test is recommended, followed-up with PSA testing in 6 to 12 months (NCCN, 2018b).

The NCCN updated prostate cancer guidelines with a chart containing guidance on the risk stratification and staging workup that note GenomeDx's Decipher, Genomic Health's Oncotype DX Prostate Cancer, Myriad Genetics' Prolaris, and Metamark's ProMark as available molecular tests for prostate cancer prognosis for men with low or favorable intermediate risk disease. They specifically state, "Men with low or favorable intermediate risk disease may consider the use of the following tumor-based molecular assays: Decipher, Oncotype DX Prostate, Prolaris, Promark. Retrospective studies have shown that molecular assays performed on prostate biopsy or radical prostatectomy provide prognostic information independent of NCCN risk groups. These include, but are not limited to, likelihood of death with conservative management, likelihood of biochemical progression after radical prostatectomy or external beam therapy, and likelihood of developing metastasis after radical prostatectomy or salvage radiotherapy (NCCN, 2018a)." Furthermore, they note that clinicians may consider testing patients for germline and somatic mutations in DNA repair genes BRCA1, BRCA2, ATM, PALB2, FANCA, and referring patients who have these mutations for genetic counseling. The NCCN noted their potential for early use of platinum chemotherapy, or eligibility for clinical trials (e.g., PARP inhibitors) in patients with low or intermediate risk disease and a strong family history or all men with

high risk, very high risk, regional, or metastatic prostate cancer. Lastly, they recommend that men with regional and metastatic disease should have tumor testing for homologous recombination gene mutations and have their tumors assessed for microsatellite instability or mismatch repair deficiency.

The NCCN also notes biomarkers as a potential avenue to improve detection rates of cancer. However, there is not enough information concerning the utility of these biomarkers as studies analyzing biomarkers' correlation with MRI results have not been performed. The NCCN has noted that the specificity may be improved in higher risk patients (such as testing in a higher risk patient whose biopsy was negative), but cannot recommend any biomarkers over another given the dearth of information regarding their validity and utility (NCCN, 2018a, 2018c).

The NCCN does include available tissue-based tests for prostate cancer prognosis within their table of possible testing as indicated in the Table below (NCCN, 2018a):

Table 1. Available Tissue-Based Tests for Prostate Cancer Prognosis

Test	Platform	Populations Studied	Outcome(s) Reported (Test independently predicts)	References	Molecular Diagnostic Services Progra Recommendations
Decipher	Whole-transcriptome 1.4M RNA expression (44,000 genes) oligonucleotide microarray optimized for FFPE tissue	Post radical prostatectomy (RP), adverse pathology/high-risk features	• Metastasis • Prostate cancer-specific mortality • Postoperative radiation sensitivity (PORTOS)	83,195,570,625-637	Cover post-RP for 1) pT2 with positive ma any pT3 disease; 3) rising PSA (above na
		Post RP, biochemical recurrence	• Metastasis • Prostate cancer-specific mortality • PORTOS		
		Post RP, adjuvant, or salvage radiation	• Metastasis • Prostate cancer-specific mortality • PORTOS		
		Biopsy, localized prostate cancer post RP or EBRT	• Metastasis • Prostate cancer-specific mortality • Gleason grade ≥4 disease at RP		
Ki-67	IHC	Biopsy, intermediate- to high-risk treated with EBRT	• Metastasis	638-641	Not recommended
		Biopsy, conservatively managed (active surveillance)	• Prostate cancer-specific mortality		
Oncotype DX Prostate	Quantitative RT-PCR for 12 prostate cancer-related genes and 5 housekeeping controls	Biopsy, low- to intermediate-risk treated with RP	• Non-organ-confined pT3 or Gleason grade 4 disease on RP	82,642,643	Cover post-biopsy for NCCN very-low-, lo favorable intermediate-risk prostate canc with at least 10 years life expectancy who received treatment for prostate cancer an candidates for active surveillance or defin
Prolaris	Quantitative RT-PCR for 31 cell cycle-related genes and 15 housekeeping controls	Transurethral resection of the prostate (TURP), conservatively managed (active surveillance)	• Prostate cancer-specific mortality	78-81,644-646	Cover post-biopsy for NCCN very-low-, lo favorable intermediate-risk prostate canc with at least 10 years life expectancy who received treatment for prostate cancer an candidates for active surveillance or defin
		Biopsy, conservatively managed (active surveillance)	• Prostate cancer-specific mortality		
		Biopsy, localized prostate cancer	• Biochemical recurrence • Metastasis		
		Biopsy, intermediate-risk treated with EBRT	• Biochemical recurrence		
		RP, node-negative localized prostate cancer	• Biochemical recurrence		
ProMark	Multiplex immunofluorescent staining of 8 proteins	Biopsy, Gleason grade 3+3 or 3+4	• Non–organ-confined pT3 or Gleason pattern 4 disease on RP	647	Cover post-biopsy for NCCN very-low- an prostate cancer in patients with at least 1(expectancy who have not received treatm prostate cancer and are candidates for ac surveillance or definitive therapy.
PTEN	Fluorescent in situ hybridization or IHC	TURP, conservatively managed (active surveillance)	• Prostate cancer-specific mortality	648-652	Not recommended
		Biopsy, Gleason grade 3+3	• Upgrading to Gleason pattern 4 on RP		
		RP, high-risk localized disease	• Biochemical recurrence		

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, 2016). 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, 2016).

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, 2018).

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. They recommend against screening with PSA for individuals under 50 or over 70, and those with a life expectancy of less than 10 – 15 years (Qaseem, Barry, Denberg, Owens, & Shekelle, 2013) .

The **American Urological Association (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)** recommends against population-based screening for prostate cancer because the reduction in mortality does not offset the harms done, such as overdiagnosis and overtreatment. ESMO also recommends against screening in asymptomatic men over 70 (Parker et al., 2015).

The **American Association of Clinical Urologists Inc. (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).

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, 2012a).

On February 13, 2012, the FDA approved the PROGENSA PCA3 Assay created by Gen-Probe Inc. From the FDA website: "The PROGENSA PCA3 Assay is an in vitro nucleic acid amplification test. The assay measures the concentration of prostate cancer gene 3 (PCA3) and prostate-specific antigen (PSA) RNA molecules and calculates the ratio of PCA3 RNA molecules to PSA RNA molecules (PCA3 Score) in post-digital rectal exam (DRE) first catch male urine specimens. The PROGENSA PCA3 Assay is indicated for use in conjunction with other patient information to aid in the decision for repeat biopsy in men 50 years of age or older who have had one or more previous negative prostate biopsies and for whom a repeat biopsy would be recommended by a urologist based on current standard of care, before consideration of PROGENSA PCA3 Assay results" (FDA, 2012b).

On December 19, 2014, the FDA approved the BRACAnalysis CDx™ created by Myriad Genetics. From the FDA website: BRACAnalysis CDx™ is an in vitro diagnostic device intended for the qualitative detection and classification of variants in the protein coding regions and intron/exon boundaries of the BRCA1 and BRCA2 genes using genomic DNA obtained from whole blood specimens collected in EDTA. Single nucleotide variants and small insertions and deletions (indels) are identified by polymerase chain reaction

(PCR) and Sanger sequencing. Large deletions and duplications in BRCA1 and BRCA2 are detected using multiplex PCR. Results of the test are used as an aid in identifying ovarian cancer patients with deleterious or suspected deleterious germline BRCA variants eligible for treatment with Lynparza™ (olaparib). This assay is for professional use only and is to be performed only at Myriad Genetic Laboratories, a single laboratory site located at 320 Wakara Way, Salt Lake City, UT 84108" (FDA, 2014) This test is commonly known as Prolaris.

A search of the FDA database on 12/27/2019 using the term "PSA" yielded 97 results. Additionally, 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: 81313, 81479, 81539, 81542, 81551, 81599, 84066, 84152, 84153, 84154, 88271, 88272, 88273, 88274, 88275, 88313, 88399, G0103, 0047U, 0005U

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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Policy Implementation/Update Information

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)