

Corporate Medical Policy

Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management AHS - M2166

File Name: gene_expression_profiling_and_protein_biomarkers_for_prostate_cancer_management
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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 progression, clinical course ranges from a microscopic tumor that never becomes clinically significant to aggressive disease that can cause metastases, morbidity, and death (Benedettini, Nguyen, & Loda, 2008; Kantoff, Tapli, & Smith, 2018).

Gene expression assays quantify specific mRNAs being transcribed to assess the genes that are active in a particular cell or tissue. Analyses of gene expression can be clinically useful for disease classification, diagnosis, prognosis, and tailoring treatment to underlying genetic determinants of pharmacologic response (Steiling, 2019). Protein expression-based assays measure the expression of the translation end-product(s) to assess cell-cycle progression. Similar to gene expression assays, protein biomarker-based assays can be clinically useful for disease classification and possible surveillance (Blume-Jensen et al., 2015; Ross, D'Amico, & Freedland, 2019).

Related Policies:

Prostate Biopsies AHS-G2007
Prostate Cancer Screening AHS-G2008
Serum Tumor Markers for Malignancies AHS-G2124

*****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

Gene expression profiling and protein biomarkers for prostate cancer management are considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

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 Gene Expression Profiling and Protein Biomarkers for Prostate Cancer is covered

Not applicable

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When Gene Expression Profiling and Protein Biomarkers for Prostate Cancer is not covered

1. The use of Prolaris®, Oncotype DX®, Promark®, or Decipher® tumor-based assays to guide management of prostate cancer is considered **investigational**.
2. The following tests to assess and/or monitor prostate cancer are considered **investigational**:
 - a. Ki-67 immunohistochemistry
 - b. *PTEN* loss

Policy Guidelines

NOTE 1: NCCN Prostate Cancer Risk Stratification and Staging Workup (NCCN, 2019b).

Risk Group	Clinical/pathologic Features	Molecular Testing of Tumor	Germline Testing
Very Low ¹	<ul style="list-style-type: none"> • T1c; AND • Gleason score ≤6/grade group 1; AND • PSA <10 ng/mL; AND • Few than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core; AND • PSA density <0.15 ng/mL/g 	Not indicated	Recommended if family history positive or intraductal histology ²
Low ¹	<ul style="list-style-type: none"> • T1-T2a; AND • Gleason score ≤6/grade group 1; AND • PSA <10 ng/mL 	Consider if life expectancy ≥10 years	Recommended if family history positive or intraductal histology ²
Favorable Intermediate ¹	<ul style="list-style-type: none"> • T2b-T2c; OR • Gleason score 3+4=7/grade group 2; OR • PSA 10-20 ng/mL; AND <ul style="list-style-type: none"> • Percentage of positive biopsy cores <50% 	Consider if life expectancy ≥10 years	Recommended if family history positive or intraductal histology ²
Unfavorable Intermediate ¹	<ul style="list-style-type: none"> • T2b-T2c; OR • Gleason score 3+4=7/grade group 2 OR Gleason score 4+3=7/grade group 3; OR • PSA 10-20 ng/mL 	Not routinely recommended	Recommended if family history positive or intraductal histology ²

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High	<ul style="list-style-type: none"> T3a; OR Gleason score 8/grade group 4 or Gleason score 4+5=9/group 5; OR PSA >20 ng/mL 	Not routinely recommended	Recommended ^{3,6}
Very High	<ul style="list-style-type: none"> T3b-T4; OR Primary Gleason pattern 5; OR >4 cores with Gleason score 8-10/grade group 4 or 5 	Not routinely recommended	Recommended ^{3,6}
Regional	<ul style="list-style-type: none"> Any T, N1, M0 	Consider tumor testing for homologous recombination gene mutations and for microsatellite instability (MSI) or mismatch repair deficiency (dMMR) ^{4,5}	Recommended ^{3,6}
Metastatic	<ul style="list-style-type: none"> Any T, Any N, M1 	Consider tumor testing for homologous recombination gene mutations and for MSI or dMMR ^{4,5}	Recommended ^{3,6}
<ol style="list-style-type: none"> For asymptomatic patients, in very low, low, and intermediate risk groups with life expectancy ≤ 5 years, no further workup or treatment is indicated until the patient becomes symptomatic. Strong family history consists of: brother or father or multiple family members diagnosed with prostate cancer at less than 60 years of age; known germline DNA repair gene abnormalities, especially <i>BRCA2</i> mutation or Lynch syndrome (germline mutations in <i>MLH1</i>, <i>MSH2</i>, <i>MSH6</i>, or <i>PMS2</i>); and/or more than one relative with breast, ovarian, or pancreatic cancer (suggests possibility of <i>BRCA2</i> mutation) or colorectal, endometrial, gastric, ovarian, pancreatic, small bowel, urothelial, kidney, or bile duct cancer (suggests possibility of Lynch syndrome). The prevalence of inherited homologous recombination gene mutations in men with metastatic or localized high risk was found to be 11.8% and 6.0%, respectively. Therefore, germline genetic testing and genetic counseling is recommended in all men with high risk, very high risk, regional, or metastatic prostate cancer (Pritchard et al., 2016). DNA analysis for MSI and IHC for MMR are different assays measuring the same biological effect. If MSI-H or dMMR is found, refer to genetic counseling to assess for the possibility of Lynch syndrome. MSI or dMMR indicate eligibility for pembrolizumab in later lines of treatment for CRPC. Consider testing for mutation in these genes (germline and somatic): <i>BRCA1</i>, <i>BRCA2</i>, <i>ATM</i>, <i>PALB2</i>, <i>FANCA</i>; refer to genetic counseling if positive. At present, this information may be used for genetic 			

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counseling, early use of platinum chemotherapy, or eligibility for clinical trials (e.g., PARP inhibitors).

6. Family history for known germline variants and genetic testing for germline variants should include *MLH1*, *MSH2*, *MSH6*, and *PMS2* (for Lynch syndrome) and homologous recombination genes *BRCA1*, *BRCA2*, *ATM*, *PALB2*, and *CHEK2*. Consider cancer predisposition NGS panel testing, which includes *BRCA2*, *BRCA1*, *ATM*, *CHEK2*, *PALB2*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Additional genes may be appropriate depending on clinical context. For example, *HOXB13* is a prostate cancer risk gene that does not have clear therapeutic implications in advanced disease, but testing may be valuable for genetic counseling.

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). In 2018, approximately 165,000 new prostate cancer diagnoses and approximately 29,000 prostate cancer deaths are expected; although, the 5-year survival rate between 2007-2013 was 99%. About 1 man in 9 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).

Prostate cancer survival is related to many factors, especially the extent of tumor at the time of diagnosis. The five-year relative survival among men with cancer localized to the prostate or with regional spread is 100%, compared with 29.3% among those diagnosed with distant metastases (Hoffman, 2018). Gene expression profiling has been proposed as a method of risk stratification for prostate cancer. Several tests evaluating the expression levels of various genes have been produced to be used in conjunction with other tools such as Gleason score and PSA assessment.

Hu et al evaluated the utility of three genomic expression classifiers (GEC), including Decipher, Oncotype, and Prolaris. 747 patients underwent GEC testing. The authors found that “Among patients with clinical favorable risk of cancer, the rate of active surveillance (AS) differed significantly among patients with a GEC result above the threshold (46.2%), those with a GEC result below the threshold (75.9%), and those who did not undergo GEC (57.9%)”. The authors further estimated that “for every nine men with favorable risk of cancer who undergo GEC testing, one additional patient may have their disease initially managed with AS (Hu 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’ objective criteria compared to the Gleason score (Cuzick et al., 2015).

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Prolaris is proposed 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 that can reliably inform providers of a course of treatment or condition. An AS status is preferable to treatment. Hu et al. used 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 clearly separated 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).

Oncotype DX

Oncotype DX is similar to Prolaris in that it assesses levels of gene expression, could be used for lower-risk patients, and could inform clinicians about the possible 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 well with BCR. They noted that OncoType DX is 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, 2019a).

OncoType DX AR-V7 Nucleus

This test evaluates the AR-V7 protein in the nucleus of circulating tumor cells and is intended to identify metastatic castration-resistant prostate cancer patients who will not respond to androgen-receptor targeted therapies (OncoType, 2019).

Scher et al examined 161 patients with progressive metastatic castration-resistant prostate cancer (mCRPC) to assess its association with AR-V7. Out of 191 samples (128 pre-ARS inhibitor and 63 pretaxane), the investigators found AR-V7-positive circulating tumor cells in 34 samples, and those samples were found to have worse clinical outcomes and overall survival than those without AR-V7. Scher et al concluded that "the results validate CTC nuclear expression of AR-V7 protein in men with mCRPC as a treatment-specific biomarker that is associated with superior survival on taxane therapy over ARS-directed therapy in a clinical practice setting (Scher et al., 2016)."

Decipher

Decipher is a genomic 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 with 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, Løppenber, Sood, Sammon, & Abdollah, 2016).

ProMark

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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).

Finally, the NCCN specifically recommends *against* two particular tests in assessment of prostate cancer; Ki-67 staining and PTEN loss (NCCN, 2019a).

Ki-67 is a nuclear protein involved in cell cycle proliferation and is intended to provide prognostic information on metastasis and prostate cancer-specific mortality (NCCN, 2019a; Ross et al., 2019). Ki-67 staining has shown some promising results. However, the primary limitation with these studies is that most active surveillance populations will have a Gleason Score of 6 or less, which is considered “low-risk”. This population will most likely have low Ki-67 levels, clouding its utility in populations trying to decide between immediate and deferred treatment (Ross et al., 2019).

PTEN loss is a relatively early event in the course of prostate cancer. PTEN is a tumor suppressor gene on chromosome 10q and is involved in cell cycle regulation. PTEN is intended to provide prognostic information on prostate cancer-specific mortality, biochemical recurrence, and cancer progression (NCCN, 2019a; Ross et al., 2019). Data on prognostic value of PTEN loss post-treatment have been conflicting. It is possible that active treatments contribute to the disruption of the PTEN pathway or the high correlation between PTEN loss and clinicopathologic factors. Lotan et al found that when clinicopathologic factors, such as Gleason Score and surgical margin status, were included in their multivariable analysis, PTEN’s association with metastasis and prostate cancer-specific mortality decreased significantly (Lotan et al., 2011).

The **National Cancer Coalition Network (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, and Myriad Genetics’ Prolaris, as available gene expression 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 or CAPRA 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, 2019a).” Furthermore, they note that clinicians may consider testing patients for germline and somatic mutations in DNA repair genes BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, and CHEK2 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 specifically does not recommend either Ki-67 or PTEN testing (NCCN, 2019a, 2019c).

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, 2019a):

Test	Platform	Recommendation
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Decipher	Whole-Transcriptome RNA expression (44000 genes), oligonucleotide microarray optimized for FFPE tissue	1.4M	Cover post-biopsy for NCCN very-low- and low-risk prostate cancer in patients with at least 10 years life expectancy who have not yet received treatment for prostate cancer and are candidates for active surveillance or definitive therapy. Cover post-RP for pT2 with positive margins, any pT3 disease, or rising PSA (above nadir)
KI-67	IHC		Not recommended
Oncotype DX	Quantitative RT-PCR for 12 prostate cancer-related genes and 5 housekeeping controls		Cover post-biopsy for NCCN very-low- and low-risk prostate cancer in patients with at least 10 years life expectancy who have not yet received treatment for prostate cancer and are candidates for active surveillance or definitive therapy.
Prolaris	Quantitative RT-PCR for 31 prostate cell cycle-related and 15 housekeeping controls		Cover post-biopsy for NCCN very-low- and low-risk prostate cancer in patients with at least 10 years life expectancy who have not yet received treatment for prostate cancer and are candidates for active surveillance or definitive therapy.
ProMark	Multiplex immunofluorescent staining of 8 proteins		Cover post-biopsy for NCCN very-low- and low-risk prostate cancer in patients with at least 10 years life expectancy who have not yet received treatment for prostate cancer and are candidates for active surveillance or definitive therapy.
PTEN	Fluorescence in situ hybridization or IHC		Not recommended

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 pursuing germline testing when appropriate is encouraged and support any further research into these tests. The AACU specifically recommends, “Tissue-based molecular testing should be considered for low and favorable intermediate risk men with life expectancy ≥ 10 years.” The **Large Urology Group Practice Association (LUGPA)** endorses this position statement by the AACU (AACU, 2018; LUGPA, 2018).

The **American Society of Clinical Oncology (ASCO)** released a guideline stating that they endorsed the non-cryotherapy 2017 joint guidelines from the **American Urological Association (AUA)/American Society for Radiation Oncology (ASTRO)/Society of Urologic Oncology (SUO)** (Bekelman et al., 2018).

Guideline 32 stated “tissue based genomic biomarkers have not shown a clear role in active surveillance for localized prostate cancer and are not necessary for follow up.” These joint guidelines also state that several

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genomic assays were validated in the pre-MRI era and that their clinical utility “remains to be established” (Sanda et al., 2018).

The AUA has also noted a “lack of predictive biomarkers to help better personalize therapy” in drug development for prostate cancer patients (AUA, 2018).

The **European Association of Urology (EAU)**, **European Society for Radiotherapy and Oncology (ESTRO)**, **European Society of Urogenital Radiology (ESUR)**, and the **International Society of Geriatric Oncology (SIOG)** released joint guidelines on prostate cancer. These guidelines stated that “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”.

These joint guidelines acknowledged both SelectMDX and ConfirmMDX as tests to select for repeat biopsies, but the guidelines noted SelectMDX as having an “uncertain role” and “probably not cost-effective”. No recommendation could be made for ConfirmMDX. Prolaris and OncoType DX were also recognized as tests that have been used to evaluate prostate cancer, but no recommendation could be made at this time (EAU, 2018).

Public Health England (PHE, 2016)

PHE notes PCA as a “promising urinary RNA biomarker” (PHE, 2016).

State and Federal Regulations, as applicable

The FDA has approved two tests for evaluation of gene expression profiles of prostate cancer as of April 2, 2019 (FDA, 2019).

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.

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

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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: 0005U, 0047U, 81479, 81541

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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Medical Director review 4/2020

Medical Director review 7/2020

Specialty Matched Consultant Panel 8/2020

Medical Director review 1/2021

Policy Implementation/Update Information

- 10/1/19 New policy developed. Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management is considered **investigational**. See **Related Policy: Prostate Cancer Screening AHS-G2008**. Medical Director review 8/2019. (lpr)
- 10/29/19 No change to policy statements. Minor reformatting and edits. (hb)
- 5/12/20 Off cycle review to align with CMP Prostate Cancer Screening AHS-G2008. Removed references to the following tests and transferred them to AHS-G2008: ExoDX Prostate, Intelliscore, Select MDX, PCA3, KLK3, ConfirmDX, PPCA. Removed CPT codes 0005U, 81313, 81551 and transferred to AHS-G2008. Updated Policy Guidelines. Medical Director review 4/2020. (lpr)
- 7/28/20 Reviewed by Avalon 2nd Quarter 2020 CAB. References updated. Medical Director review 7/2020. (lpr)
- 9/8/20 Specialty Matched Consultant Advisory Panel review 8/19/2020. No changes to policy statement. (lpr)
- 2/9/21 Added PLA code 0005U to Billing/Coding section. Off-cycle review per Avalon, No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber

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