Corporate Medical Policy

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

File Name: gene_expression_profiling_and_protein_biomarkers_for_prostate_cancer
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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 et al., 2008; Taplin, & Smith, 2022).

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 & Christenson, 2021). 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 et al., 2021).

******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 gene expression profiling and protein biomarkers for prostate cancer when it is determined to be medically necessary because the medical criteria and guidelines shown 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 Gene Expression Profiling and Protein Biomarkers for Prostate Cancer is covered

1. For individuals with low-risk or favorable intermediate-risk disease, as defined by the NCCN (See Note 1), the one-time use of Prolaris®, Oncotype DX®, OR Decipher® tumor-based assays to guide management of prostate cancer is considered medically necessary when **ALL** of the following criteria are met:
   a. A needle biopsy showed localized adenocarcinoma of the prostate with no clinical evidence of metastasis or lymph node involvement;
   b. The individual has no significant co-morbidities, including advanced age, to suggest they have an estimated life expectancy of less than 10 years.

2. For individuals with unfavorable intermediate-risk and high-risk disease, as defined by the NCCN (see Note 1), the one-time use of Prolaris® or Decipher® tumor-based assays to guide management of prostate cancer is considered medically necessary when **ALL** of the following conditions are met:

   a. A needle biopsy showed localized adenocarcinoma of the prostate with no clinical evidence of metastasis or lymph node involvement;
   b. The individual has no significant co-morbidities, including advanced age, to suggest they have an estimated life expectancy of less than 10 years.

3. For individuals for whom there is a potential need for a prostate biopsy, the one-time use of the EPI biomarker test prior to initial prostate biopsy is considered medically necessary when **ALL** of the following conditions are met:

   a. The individual has confirmed (See Note 2) moderately elevated PSA levels:

      i. For individuals ages 50 – 75 years, PSA levels between 3 – 10 ng/mL
      ii. For individuals over the age of 75, PSA levels between 4 – 10 ng/mL

   b. The individual has none of the following conditions for which a prostate biopsy is already indicated:

      i. DRE suspicious for cancer.
      ii. Persistently elevated PSA.
      iii. Positive multiparametric MRI, if performed.
      iv. Known to have a high-penetrance prostate cancer risk gene(s) per NCCN guidelines (See Note 3)

   c. The individual has no other relative contraindication for prostate biopsy including ANY of the following:

      i. <10-year life expectancy.
      ii. Benign disease not ruled out.

4. For individuals with a prostate, the use of the 4Kscore test once (either once prior to initial biopsy or once prior to repeat biopsy) is considered medically necessary when **ALL** of the following conditions are met:

   a. The individual has confirmed (see Note 2), moderately elevated PSA levels:

      i. For individuals ages 45 – 75 years, PSA levels greater than 3 and less than 10 ng/mL.
      ii. For individuals over the age of 75, PSA levels greater than or equal to 4 and less than 10 ng/mL.

   b. The individual has none of the following conditions for which a prostate biopsy is already indicated:

      i. DRE suspicious for cancer.
      ii. Persistently elevated PSA.
      iii. Positive multiparametric MRI (if performed).
      iv. Ethnicity at higher risk for prostate cancer (see Note 4).
      v. First-degree relative (see Note 5) with prostate cancer.
      vi. Known to have a high-penetrance prostate cancer risk gene(s) per NCCN guidelines (see Note 3).

c. No other relative contraindication for prostate biopsy including ANY of the following:

i.<10-year life expectancy.
ii.Benign disease not ruled out.

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

1. For the assessment and/or monitoring of prostate cancer, the following tests are considered not medically necessary:
   a. Ki-67 immunohistochemistry
   b. *PTEN* loss

2. The following tests are considered not medically necessary, including, but not limited to:

   - All other urine testing for gene expression profile and/or protein biomarkers designed to assess prostate cancer.

   - Other screening tests for prostate cancer, including, but not limited to, alpha-methylacyl coenzyme A racemase (AMACR), 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, MyProstateScore, IsoPSA®,gene hypermethylation, *PCA3/KLK3* (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate-specific antigen]) ratio, Prostate Health Index (PHI), PCA3 score or ConfirmMDx.

   - All other tests not described above that use cellular and biologic features of a tumor, including those used to predict risk of recurrence in patients with prostate cancer.

Reimbursement is not allowed for 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).

NOTE 1: NCCN Prostate Cancer Initial Risk Stratification and Staging Workup for Clinically Localized Disease (NCCN, 2022a).

Risk Group	Clinical/Pathological Features
Very Low	Has all of the following: · cT1c; AND · Grade Group 1 · PSA <10 ng/mL · Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core · PSA density <0.15 ng/mL/g
Low	Has all of the following but does not qualify for very low risk: · cT1-cT2a · Grade Group 1 · PSA <10 ng/mL

<table>
<tr><td rowspan="3">Intermediate</td><td rowspan="3">Has all of the following:
· No high-risk group features
· No very-high-risk group features
· Has one or more intermediate risk factors
» cT2b-cT2c
» Grade Group 2 or 3
» PSA 10-20 ng/mL</td><td>Favorable Intermediate</td><td>Has all of the following:
· 1 IRF
· Grade Group 1 or 2
· <50% biopsy cores positive</td></tr>
<tr><td>Unfavorable Intermediate</td><td>Has one or more of the following:
· 2 or 3 IRFs
· Grade Group 3
· ≥50% biopsy cores positive</td></tr>
<tr><td>High</td><td colspan="2">Has no very-high-risk features and has at least one high-risk feature:
· cT3a OR
· Grade Group 4 or Grade Group 5 OR
· PSA >20 ng/mL</td></tr>
<tr><td>Very High</td><td colspan="2">Has at least one of the following:
· T3b-T4
· Primary Gleason pattern 5
· 2 or 3 high-risk features
· >4 cores with Grade Group 4 or 5</td></tr>
</table>

NOTE 2: PSA elevation should be verified after a few weeks under standardized conditions (e.g., no ejaculation, manipulations, and urinary tract infections, no medications such as 5α-reductase) in the same laboratory or other Clinical Laboratory Improvement Amendments (CLIA) approved laboratory before considering a biopsy.

NOTE 3: According to the NCCN Prostate Cancer Early Detection guidelines, the main high-penetrance cancer risk genes include *BRCA1, BRCA2, ATM, MLH1, MSH2, MSH6, HOXB13, CHEK2, NBN, PALB2, RAD51D,* and *TP53* (NCCN, 2022b).

NOTE 4: According to the NCCN Prostate Cancer Early Detection guidelines, "African-American men, men with a family history of prostate cancer, and those with a known genetic predisposition represent high-risk groups (NCCN, 2022b)."

NOTE 5: First-degree relatives include parents, full siblings, and children of the individual.

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 et al., 1997; Tabayoyong & Abouassaly, 2015). In 2021, the American Cancer Society estimates that approximately 248,530 new prostate cancer diagnoses and approximately 34,130 prostate cancer deaths will occur; although, the 5-year survival rate between 2007-2013 was 99%. About 1 man in 8 will be diagnosed with prostate cancer during his lifetime in the United States (ACS, 2021; Siegel et al., 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 aged 55 or older and approximately 60 percent of men by age 80 (Bell et al., 2015). These data suggest that prostate cancer often grows so slowly that most men die of other causes before the disease becomes clinically advanced (Hoffman, 2021).

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 31% among those diagnosed with distant metastases (Hoffman, 2021). 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. The Gleason score is a scoring system used to categorize a prostate cancer biopsy based on risk assessment.

Tissue-based gene expression classifiers (GEC) are now widely used to assist in prostate cancer prognosis. These tests are RNA-based prognostic biomarkers that analyze a distinct multigene panel to predict cancer progression, from the chance of having the disease to the probability of death at ten years due to prostate cancer. Genomic tests can predict prostate cancer aggressiveness, detect potentially dangerous prostate cancer-related genomic activity, and utilize biopsy samples to deliver prognostic information via immunofluorescence imaging. Additionally, researchers have identified the potential of microRNAs as human prostate cancer biomarkers (Song et al., 2018). While several types of biomarker tests exist, the NCCN specifically recommends Prolaris, Oncotype DX Prostate, Decipher, and ProMark as tumor-based molecular assays to consider during initial risk stratification (NCCN, 2022a). Ki-67 and PTEN are also listed in NCCN guidelines, but are not recommended (NCCN, 2022a).

Proprietary Testing, Clinical Utility and Analytical Validity

Hu et al. (2018) 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 and can provide important pretreatment prognostic information. Cuzick et al. (2015) 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).

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. (2018) 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. (2018) 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 Carneiro 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).

Tward et al. (2020) studied the ability of CCR to predict prostate cancer metastasis using Prolaris. According to a CCR threshold of 2.112, 29.5% patients were hypothesized to be high risk metastasis (CCR>2.112) and 70.5% were unfavorable intermediate risk patients (CCR < 2.112). Patients were followed five years later to determine if CCR accurately predicted metastasis in men undergoing multimodality therapy (androgen deprivation with surgery) or radiation therapy. According to the results, the CCR score does provide a clinically meaningful different risk of metastasis for patients receiving multimodality therapy or radiation therapy. Multimodality therapy reduced patients' risk of metastasis and treatment benefit can be evaluated as a function of the CCR score. For those with CCR scores below the threshold of 2.112 (27% of high-risk group and 73% of the unfavorable intermediate group), radiation therapy was considered after assessing the difference in the risk of metastasis (Tward et al., 2020).

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 genomic prostate score (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. (2015) found that the GPS score correlated well with BCR. The researchers 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, 2022a). Oncotype DX was recently validated in a group of men separated by race, showing that this tool is an independent predictor of adverse pathology with similar predictive accuracy in both African American (n=96) and European American (n=76) men (Murphy et al., 2020).

OncoType DX AR-V7 Nucleus

The OncoType DX AR-V7 Nucleus evaluates the Androgen Receptor Splice Variant-7 (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, 2021).

Scher et al. (2016) 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. (2016) 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).

Further, Chen et al. (2018) studied the overexpression of the nuclear AR-V7 protein in prostate cancer cases. A total of 401 men participated in this study. Participants were split into two cohorts: cohort I included those who were high-risk (n=238), and cohort II included those who were not considered high-risk (n=238). Analyses showed that high nuclear AR-V7 protein expression was detected in approximately 30-40% of participants, and a "High baseline expression of nuclear AR-V7 protein was associated with an unfavorable BCR-free survival in the high-risk patient cohort I but not in the unselected consecutive cohort II. Remarkably, AR-V7 was an independent negative prognostic factor in high-risk prostate cancer patients of cohort I who were selected to receive adjuvant treatment" (Chen et al., 2018).

Graf et al. (2020) studied the clinical utility of AR-V7 as a biomarker for patients with progressing metastatic castration-resistant prostate cancer (mCRPC). The results were used by physicians to make a second line of therapy choice of either an androgen receptor signaling inhibitor (ARSI) or taxane chemotherapy. 255 samples of circulating tumor cells (CTCs) were tested for AR-V7. Patients with detectable AR-V7 in the CTCs had superior survival with taxane treatment over ARSIs and patients who were AR-V7- negative had superior survival on ARSIs over taxanes. These results showed that men who tested AR-V7- positive were more likely to survive longer on taxane chemotherapy. Overall, the authors suggest that the use of AR-V7 CTC test "to inform treatment choice can improve patient outcomes relative to decisions based solely on standard-of-care measures" (Graf et al., 2020).

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, et al., 2016).

Van den Broeck et al. (2019) aimed to validate the Decipher test in the prediction of distant metastatic recurrence in men with high-risk nonmetastatic prostate cancer 10 years after the surgery was completed. A total of 298 men participated in this study. Results showed that "the median Decipher scores were higher in the population that developed metastases" suggesting that this study "validates Decipher as a predictor for metastatic recurrence even in patients with high-risk, nonmetastatic PC [prostate cancer] within 10-yr follow-up (Van den Broeck et al., 2019)." Specifically, the data showed that each 10% increase in Decipher score resulted in an increased risk of distant metastatic prostate cancer recurrence.

In a prospective trial by Marascio et al. (2020), the clinical utility of the Decipher tumor test on postoperative management of prostate cancer post prostatectomy was discussed. 3,455 males were enrolled in the study and the change in treatment decision-making was recorded. In the cohort, 61% of the patients had high-risk tumors with a two-year prostate cancer reoccurrence. As a result of genome classifier testing, providers' recommendations changed for 39% of the patients, translating to a number needed to test of three to change one treatment decision. This study demonstrated that genome classifier testing favorably impacts treatment decision making post radical prostatectomy, promoting more post-operative radiotherapy. This translated to improved patient reported quality of life (Marascio et al., 2020).

ExoDX Prostate (IntelliScore)

ExoDX is a urinary test that detects the expression level of three genetic biomarkers (ERG, PCA3, and SPDEF) (ExoSome, 2019, 2021). This test integrates the expression levels of these three biomarkers and assigns an individualized risk score to predict the risk of high-grade prostate cancer (Gleason score ≥7). This test is intended for men 50 or over with a PSA level of 2-10 ng/mL presenting for an initial biopsy (prior to a DRE) (ExoSome, 2019, 2021).

McKiernan et al. (2016) used ExoDX to discriminate between benign prostate cancer (Gleason score 6 and under) and high-risk cancer (Gleason score ≥7). The prognostic score was derived from a sample of 499 patients with PSA levels of 2-20 ng/mL; it was then validated in a sample of 1064 patients and evaluated in a population of 255. The test was compared to the standard of care practices (SOC), and the area under the curve (AUC) of the test was 0.77 compared to the SOC's 0.66. An independent validation found the AUC of the test to be 0.73 compared to the SOC's 0.63. The authors calculated that 138 of 519 biopsies (27%) would have been avoided and that the test only missed 5% of patients with high-risk disease (McKiernan et al., 2016). Within a second phase of the long-term study, McKiernan and colleagues report that using the EPI validated cut-point of 15.6 results in avoiding 26% of unnecessary prostate biopsies and a 20% decrease in all biopsies. If the EPI cut-point is raised to 20, then 31% of total biopsies would be avoided, including 40% of unnecessary biopsies (McKiernan et al., 2018).

A study published in 2018 did a cost-effectiveness analysis and comparison of not only ExoDx (EPI), but also Prostate Health Index (PHI), 4Kscore, and SelectMDx to current standard care of care. Using 2017 US dollars for their calculations, the cost and quality adjusted life-years (QALY) for the current standard of care—transrectal ultrasound guided biopsy (TRUS biopsy)—was $3,863 and 18.0865, respectively. The authors of the study note that EPI, PHI, and SelectMDx cost less than performing TRUS biopsy. They note, "The EPI provided the highest QALY with an incremental cost-effectiveness ratio of $58,404 per QALY. The use of biomarkers could reduce the number of unnecessary biopsies by 24% to 34% compared to the current standard of care… Using SelectMDx or the EPI following elevated prostate specific antigen but before proceeding to biopsy is a cost-effective strategy in this setting" (Sathianathen Niranjan et al., 2018).

A randomized, blinded, two-armed clinical utility study was published in 2020 using ExoDx (EPI) in individuals presenting for initial biopsy with PSA values in the intermediate range (2 – 10 ng/mL). This large study (n = 1,094) included 72 urologists from 24 different practices. All patients had an EPI test performed, but the patients were divided into two different groups (control and experimental) where only the experimental group received results prior to their biopsy decision. Of the individuals within the experimental group who received negative EPI scores, 74% deferred biopsy. For individuals within the experimental group who received positive EPI scores, 87% were recommended by their urologists to undergo the biopsy, and ultimately 72% did. As compared to the control arm of the study, there is a 30% increase in the detection of high-grade prostate cancer [HGPC], and the authors "estimate that 49% fewer HGPC were missed due to deferrals compared to standard of care (SOC). Overall, 68% of urologists reported that the EPI test influenced their biopsy decision" (Tutrone et al., 2020).

4Kscore

4Kscore is intended to assess the risk for "aggressive" prostate cancer. The test incorporates total PSA, free PSA, "intact" PSA, and "hk2" [human kallikrein 2] (NCCN, 2022a; OPKO, 2021). These biomarkers, along with other patient clinical information (such as age and prior biopsy status) are evaluated by the 4Kscore algorithm, which generates a risk score for aggressive cancer (%risk of Gleason 7 or higher, if a biopsy were to be performed).

Zappala et al. (2017) performed a meta-analysis of 4kScore validation studies. A total of 12 studies encompassing 11134 patients were included, and the pooled area under curve (AUC) for the test to "discriminate for high-grade PCa [prostate cancer] was found to be 0.81 (Zappala et al., 2017).

Two key prospective and blinded investigations were completed in 2015 and 2018, attempting to validate 4Kscore in a total of 937 patients, defined as the "intended use" population. The test demonstrated an overall sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of 96.9%, 27.4%, 95.9%, and 33.7%, respectively. These metrics showed little variation between African American and non-African American individuals, with the exception of PPV (46.7% compared to 28.1%, respectively) (Parekh et al., 2015; Punnen et al., 2018).

Wysock et al. (2020) compared the performance of 4K score to SelectMDx in detecting prostate cancer in 114 patients who received both tests. These tests were analyzed to provide guidance on whether to perform biopsy. Based on the results, the two scores lead to different biopsy recommendations. 50 of the 144 patients underwent biopsy based on the test results. 22 of the 50 patients (44%) were found to have clinically significant prostate cancer. In addition, the specificity of 4K score was significantly greater compared to SelectMDx while sensitivity was similar. The area under the curve for 4K score was 0.830 and SelectMDx was 0.672. The authors state that "the 4Kscore when combined with magnetic resonance imaging was superior to the SelectMDx" in detecting prostate cancer (Wysock et al., 2020).

Mi et al. (2021) completed a meta-analysis to help inform the diagnostic accuracy of 4Kscore in detecting high-grade prostate cancer, covering a total of 9 studies and 1,689 patients. The investigators reported a pooled sensitivity, specificity, and AUC of 0.90 (95%CI: 0.86-0.92), 0.44 (95%CI: 0.36-0.52), and 0.81 (95%CI: 0.77-0.84), respectively, and concluded that "4Kscore can be used as a model for the diagnosis of high-grade CaP [prostate cancer]. However, we detected significant heterogeneity among studies that was not explained by subgroup or meta-regression analysis, thus lowering our confidence in these results."

Further validation of the test will be useful; however to date, 4Kscore has demonstrated relatively high sensitivity and AUC compared to other molecular testing for the assessment of high-grade prostate cancer risk.

ConfirmMDX

ConfirmMDX uses methylation-specific polymerase chain reaction (PCR) to identify methylation of three genes (*GSTP1*, *APC*, and *RASSF1*), and determine whether a patient with a previously negative prostate biopsy should undergo a repeat biopsy (MDx_Health, 2022a). This test has been evaluated by Van Neste, Partin, et al. (2016) and was found to have a negative predictive value (NPV) of 96% for high-grade prostate cancer. A total of 7899 prostate core biopsies from 803 patients were assessed, and the NPV of finding low levels of DNA methylation was 89.2% for all cancers. The positive predictive value (PPV) of the genetic assay was found to be 28.2% (for detection of any cancer on a repeat biopsy), and this was calculated to be "significantly higher" than the PPV of standard of care practices. The final algorithm was optimized to a maximum of 0.742 AUC (Van Neste, Partin, et al., 2016). Wojno et al. (2014) evaluated the utility of this test and found that out of 138 patients that the test had been performed on, only 6 with a negative result had undergone a repeat biopsy.

SelectMDX

SelectMDX evaluates two mRNA cancer-related biomarkers (HOXC6 and DLX1 with *KLK3* as a reference gene) to assist a clinician in deciding to continue routine screening or to order a prostate biopsy. This test is considered a "non-invasive urine test" and reports a binary result of "increased risk" or "very low risk" (MDx_Health, 2022b). Van Neste, Hendriks, et al. (2016) evaluated this test at a 0.90 AUC in a validation cohort. The authors concluded that the mRNA signature was one of the most significant components of the validation results (Van Neste, Hendriks, et al., 2016). Shore (2018) assessed the effect of SelectMDX results on clinical decision making and found that out of 253 patients that SelectMDX evaluated as "negative," only 12% underwent a biopsy (Shore, 2018).

IsoPSA®

IsoPSA® is a blood test indicated for use in men over 50 years of age with elevated PSA, to help inform the likelihood of having high-grade prostate cancer. Utilizing a proprietary, 2-phase aqueous polymer and salt mixture, PSA isoforms separate between the two aqueous phases, where the discriminatory power between benign and cancerous clinical phenotypes purportedly resides primarily in the top phase. The PSA isoform content in the top layer is then measured with conventional, FDA-approved PSA ELISA immunoassays, and a single numerical score (IsoPSA Index) that is either above or below an established cutoff is generated, providing a binary positive or negative result.

The clinical validity of IsoPSA® was demonstrated in several studies. Stovsky et al. (2019) performed a multicenter, prospective validation in 271 men scheduled for prostate biopsy, and found that the test yielded an area under the receiver operating characteristic curve of 0.784 for high grade cancer. Klein et al. (2022) completed an additional multicenter study of 888 men scheduled for prostate biopsy and found similar results, establishing an AUC of 0.783 for IsoPSA®. These investigators further reported a sensitivity, specificity, NPV, and PPV of 0.902, 0.455, 0.893, and 0.477, respectively.

To investigate the clinical utility of IsoPSA®, Scovell et al. (2022) performed a "real-world" observational study engaging 38 providers across the Cleveland Clinic health system. The authors examined whether an IsoPSA® result changed the number of biopsy and magnetic resonance imaging recommendations for a cohort of 734 individuals with total serum prostate specific antigen [PSA] ≥4 and <100 ng/ml and no history of prostate cancer. The authors determined that "IsoPSA testing resulted in a 55% (284 vs 638) net reduction in recommendations for prostate biopsy for men with total PSA ≥4 ng/ml."

Progensa PCA3

Progensa *PCA3* is an FDA-approved assay that examines the concentration of the prostate cancer gene 3 (*PCA3*) and compares it to the amount of prostate-specific antigen RNA. This test is intended for assistance in decision making for a repeat biopsy in men 50 years or older, and a *PCA3* score under 25 was associated with a decreased likelihood of a positive biopsy. However, the manufacturer states this test should not be used for men with atypical small acinar proliferation on their most recent biopsy (Hologic, 2017). A total of 466 samples were provided, and 102 of these samples were evaluated to require a repeat biopsy. This assay was evaluated at a 77.5% sensitivity, a 57.1% specificity, a 33.6% positive predictive value, and a 90.0% negative predictive value (Gittelman et al., 2013).

Rodríguez and García-Perdomo (2020) performed a systematic review and meta-analysis of the diagnostic accuracy of PCA3 prior to a patient's first prostate biopsy. They found that with a cutoff of 35, the sensitivity of the diagnostic tests was 0.69 (95% confidence interval 0.61-0.75), specificity was 0.65 (95% confidence interval 0.553-0.733), the diagnostic odds ratio was 4.244 (95% confidence interval 3.487-5.166), and the AUC was 0.734 (95% confidence interval 0.674-0.805). This study suggests that there may be a greater clinical utility with 35 as the cutoff as opposed to the 25 approved by the FDA, and ultimately urinary PCA3 can "be used as a guide for directing the performance of the first prostate biopsy and decreasing unnecessary biopsies" (Matuszczak et al., 2021; Rodríguez & García-Perdomo, 2020).

MyProstateScore

MyProstateScore is a panel that measures urinary prostate cancer antigen 3 (PCA3), urinary TMPRSS2:ERG gene fusion (T2:ERG), and serum PSA, to predict the likelihood of prostate cancer in biopsy-naïve patients. Validating the test in a cohort of 1225 patients, Tomlins et al. (2016) found that MyProstateScore was superior to PSA alone, yielding an AUC of 0.693 (compared to 0.585 for PSA). Tosoian et al. (2021) aimed to validate an optimal MyProstateScore threshold for ruling out clinically significant (grade group ≥2) cancer, and determined that a threshold of 10 resulted in 97% sensitivity and 98% NPV. The investigators further concluded that use of the test could have prevented about 1/3 of the biopsies that patients received.

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. (2015) 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).

Prostate Health Index

Prostate Health Index (PHI) measures total PSA, fPSA (free non-protein bound PSA), and p2PSA (an isoform of fPSA). Levels of these three proteins are combined and calculated, implying that men with a higher total PSA and p2PSA and a lower fPSA have a higher risk of presenting with prostate cancer (Couñago et al., 2020). PHI is clinically used to reduce the number of unnecessary biopsies in men with border-line PSA levels, predict biochemical recurrence after radical prostatectomy, and enhance the predictive value of multi-parametric MRI. PHI is not recommended in primary screening for prostate cancer (Duffy, 2020).

Jia et al. (2020) compared the diagnostic value of PCA3 and PHI for detection of prostate cancer at initial biopsy in a meta-analysis of 10,376 patients from 20 studies. The pooled sensitivity for PCA3 and PHI was 0.55 and 0.88, respectively. The pooled specificity for PCA3 and PHI was 0.74 and 0.36. The area under the curve, measuring

overall quality of the diagnostic test, was 0.72 for PCA3 and 0.76 for PHI. The combination use of PCA3 and PHI resulted in a higher area under the curve of 0.79. Overall, this study suggests that both PCA3 and PHI show acceptable results and a "combination of these two diagnostic tests may be more helpful than the use of either test alone in prostate cancer management" (Jia et al., 2020).

White et al. (2018) evaluated the clinical utility of the PHI on "biopsy decision management" among patients with "non-suspicious DRE findings and tPSA in the 4-10 ng/mL range" in a observational study at several large urology group practices. They found that there was a "significant reduction in biopsy procedures performed" in men receiving a PHI test when comparing to the control group (36.4% biopsy vs 60.3% biopsy), and that the "PHI score impacted physician's patient management plan in 73% of cases, including biopsy deferrals when the PHI score was low, and decisions to perform biopsies when the PHI score indicated an intermediate or high probability of prostate cancer," defined as a score greater than or equal to 36. This altogether conveyed the importance of the PHI score in clinical decision making in terms of how to proceed with individual patient circumstances (Matuszczak et al., 2021; White et al., 2018).

Ki-67 and PTEN

Finally, the NCCN specifically recommends *against* two particular tests in assessment of prostate cancer; Ki-67 staining and PTEN loss (NCCN, 2022a).

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, 2022a; Ross et al., 2021). 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., 2021).

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, 2022a; Ross et al., 2021). 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. (2011) 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.

Guidelines and Recommendations

National Cancer Coalition Network (NCCN)

Patients with low or favorable intermediate-risk disease and life expectancy ≥10 y may consider the use of the following tumor-based molecular assays: Decipher, Oncotype DX Prostate, and Prolaris. Patients with unfavorable intermediate- and high-risk disease and life expectancy ≥10 y may consider the use of Decipher and Prolaris tumor-based molecular assays. Retrospective studies have shown that molecular assays performed on prostate biopsy or RP specimens 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 recurrence after radical prostatectomy, and likelihood of developing metastasis after operation, definitive EBRT, or post-recurrence EBRT" (NCCN, 2022a). Furthermore, they note that clinicians may consider testing patients with metastatic prostate cancer and regional prostate cancer for alterations in homologous recombination DNA repair genes *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*, and *CDK12*; "Post-test genetic counseling is recommended if pathogenic/likely pathogenic somatic mutations in any gene that has clinical implications if also identified in germline (eg, *BRCA2*, *BRCA1*, *ATM*, *PALB2*, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, *PMS2)* (NCCN, 2022a)." The NCCN noted that somatic tumor testing of the aforementioned genes has potential for early use of platinum chemotherapy, use of PARP inhibitors, or eligibility for clinical trials. Lastly, they recommend that men with regional disease, metastatic castration-resistant disease, or

castration-naïve metastatic disease should additionally consider tumor testing for microsatellite instability or mismatch repair deficiency. The NCCN also specifically does not recommend either Ki-67 or *PTEN* testing (NCCN, 2022a).

The NCCN does include available tissue-based tests for prostate cancer prognosis within their table of possible testing as indicated in the Table below. Regarding Decipher testing, NCCN states that Decipher "may be considered to inform adjuvant treatment if adverse events are found to occur after radical prostatectomy". Decipher testing can also be used to inform counseling for risk stratification in patients with PSA resistance or reoccurrence after radical prostatectomy. NCCN discourages repeat molecular tumor analysis (NCCN, 2022a, 2022b):

Test	Platform	Recommendation
Decipher	Whole-Transcriptome 1.4M RNA expression (46,050 genes), oligonucleotide microarray optimized for FFPE tissue	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.
PTEN	Fluorescence in situ hybridization or IHC	Not recommended

The NCCN, within the algorithm for the indications for prostate biopsy, says to "consider biomarkers that improve the specificity of screening" for individuals who have had elevated levels of PSA (above 3 ng/mL for those ages 45 – 75 years or 4 ng/mL or higher for those individuals over the age of 75 years. The NCCN goes on to state, "Biomarkers that improve the specificity of detection are not, as yet, mandated as first-line screening tests in conjunction with serum PSA. However, there may be some patients who meet PSA standards for consideration of prostate biopsy, but for whom the patient and/or the physician wish to further define risk. Percent-free may improve cancer detection. The probability of high-grade cancer (Gleason score > 3+4, Grade Group 2, or higher) may be further defined utilizing the SelectMDx, 4Kscore, Prostate Health Index (PHI), and ExoDx Prostate test. Extent of validation of these tests across diverse populations is variable. It is not known how such tests could be

applied in the optimal combination with MRI as yet (NCCN, 2022b)." The NCCN notes that these tests- including percent-free PSA, 4Kscore, PHI, PCA3, and ConfirmMDx-improve specificity in the post-biopsy setting and it should be considered in patients who are thought to be at higher risk despite a negative prostate biopsy (NCCN, 2022b).

The NCCN panel remarks that 4Kscore "can be considered for patients prior to biopsy and for those with a negative biopsy who are thought to be at higher risk for clinically significant prostate cancer" The NCCN further remarks that SelectMDx is "potentially informative" in patients who have never undergone biopsy and can therefore be "considered" in these patients. The NCCN also acknowledged that ConfirmMDX and PCA3 can be considered an option for men contemplating repeat biopsy and is approved for limited coverage by MolDX to reduce unnecessary repeat biopsies. Further, ExoDx *Prostate (IntelliScore)*, also called EPI, "can be considered as an option for men contemplating initial or repeat biopsy" (NCCN, 2022b).

American Society of Clinical Oncology (ASCO)

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

In 2020, an ASCO multidisciplinary panel published guidelines on molecular biomarkers in localized prostate cancer. These guidelines are below:

- "Commercially available molecular biomarkers (ie, Oncotype Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended
- Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered
- The Expert Panel recommends consideration of a commercially available molecular biomarker (eg, Decipher Genomic Classifier) in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. In the absence of prospective clinical trial data, routine use of genomic biomarkers in the postprostatectomy setting to determine adjuvant versus salvage radiation or to initiate systemic therapies should not be offered.
- "In men with newly diagnosed prostate cancer who are eligible for active surveillance, both genomics and MRI intend to identify clinically significant cancers. The Expert Panel endorses their use only in situations in which the result, when considered as a whole with routine clinical factors, is likely to have an impact on patient management. This may include, for instance, the initial management of men potentially eligible for active surveillance, in whom each of these approaches may provide clinically relevant and actionable information. These tests may provide information independent of routine clinical parameters and independent of one another" (Eggener et al., 2020).

In 2020, an ASCO panel published guidelines on the use of molecular biomarkers in localized prostate cancer. In concordance with the 2018 and 2019, ASCO recommends the use of commercially available tests (Oncotype Dx Prostate, Prolaris, Decipher, and ProMark) when the assay result "is likely to have an impact on patient management. Examples include select men with high-volume low-risk or favorable intermediate-risk prostate cancer who are considering active surveillance or in men with high-risk features for treatment intensification. While testing may influence management decisions, there is no high-level evidence that the results from these panels will improve quality of life or cancer-specific outcomes (Scott E. Eggener et al., 2020).

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)**

The EAU, ESTRO, ESUR and 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 (Strong);
- imaging (Strong);
- an additional serum or urine-based test (Weak)."

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, 2021).

In 2021, updated joint guidelines acknowledged five commercially available tests (Oncotype Dx, Prolaris, Decipher, Decipher PORTOS and ProMark). Since the long-term impact of the use of these tests is unproven, the panel concluded that "these tests should not be offered routinely, but only in subsets of patients where the test result provides clinically actionable information, such as for instance in men with favourable intermediate-risk PCa who might opt for AS or men with unfavourable intermediate-risk PCa at RP to decide on treatment intensification with hormonal therapy" (HT) (EAU, 2021).

European Society for Medical Oncology (ESMO)

ESMO provided recommendations on the use of precision medicine in providing prognostic information for prostate cancer. These are the following recommendations provided:

- ESMO does not recommend the use of AR-V7 testing, stating that the test is of limited value in therapy selection.
- Other tissue-based molecular assays may be used on conjunction with clinicopathological factors to make treatment decision.
- Germline testing for *BRCA2* and other DDR [DNA damage and repair] genes is recommended in patients with a family history of cancer and should be considered in patients with metastatic cancer (Parker et al., 2020).

State and Federal Regulations, as applicable

Food and Drug Administration (FDA)

On November 6, 2020, the FDA approved FoundationOne CDx, by Foundation Medicine, Inc. This device is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 311 genes, rearrangements in 3 genes, and copy number alterations in 3 genes. FoundationOne CDx also utilizes circulating cell-free DNA collected in FoundationOne® Liquid CDx Blood Sample Collection Kit to identify patients with non-small cell lung cancer, prostate cancer, ovarian cancer, or breast cancer who may benefit from treatment with the targeted therapies. This test provides tumor mutation profiling of *BRCA1*, *BRCA2*, and ATM alterations for prostate cancer diagnosis (FDA, 2020).

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, 2012).

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.

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, 81541, 81542, 81551, 0005U, 0021U, 0047U, 0053U, 0228U, 0339U, 0359U, 0403U

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

For Policy Titled: Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

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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

For Policy Titled: Gene Expression Profiling and Protein Biomarkers for Prostate Cancer

Medical Director review 4/2021

Specialty Matched Consultant Panel 8/2021

Medical Director review 4/2022

Medical Director review 1/2023

Policy Implementation/Update Information

For Policy Titled: Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

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 change 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)

For Policy Titled: Gene Expression Profiling and Protein Biomarkers for Prostate Cancer

5/18/21 Reviewed by Avalon 1st Quarter 2021 CAB. Medical Director review 4/2021. Revised "When Covered" section to include tests to assess and/or monitor prostate cancer which were relocated from AHS-G2008 Prostate Specific Antigen (PSA) Testing policy. These tests remain investigational. Updated Policy Guidelines, Billing/Coding sections as well as References. Changed related policy AHS-G2008 Prostatic Specific Antigen (PSA) Testing title. **Policy Title changed from: Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management to: Gene Expression Profiling and Protein Biomarkers for Prostate Cancer.** (lpr)

9/7/21 Specialty Matched Consultant Advisory Panel review 8/18/2021. No change to policy statement. (lpr)

2/8/22	Reviewed by Avalon Q4 2021 CAB. Removed PLA code 0244U from Billing/Coding section. Medical Director review 1/2022. No change to policy statement. (lpr)
5/31/22	Reviewed by Avalon Q1 2022 CAB. Extensive revisions to policy. Added coverage criteria under "When Covered" section. Updated policy guidelines and references. Medical Director review 4/2022. (lpr)
9/30/22	Added CPT code 0339U to Billing/Coding section. Corrected typo in policy statement. No change to intent of policy statement. (lpr)
12/30/22	Added PLA code 0359U to Billing/Coding section for effective date 1/1/2023. (lpr)
3/31/23	Off cycle review by Avalon. Updated policy guidelines and references. Deleted related policies section. Clarified "when covered" section and added coverage criteria for 4Kscore. Clarified and edited notes 2-5. Added PLA codes 0339U, 0359U to Billing/Coding section. Medical Director review 1/2023. (lpr)
9/29/23	Added PLA code 0403U to Billing/Coding section for 10/1/23 code update. (lpr)