Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

Policy Number: **AHS – M2166 – Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management**

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**Policy Description**

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, 2020).

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, 2019b).

**Related Policies**

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**Indications and/or Limitations of Coverage**

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request.

1. The use of Prolaris®, Oncotype DX®, Promark®, OR Decipher® tumor-based assays to guide management of prostate cancer is considered medically necessary only if **ALL** the following criteria have been met:
a. Needle biopsy with localized adenocarcinoma of prostate with no clinical evidence of metastasis or lymph node involvement; AND

b. No presence of significant co-morbidities, including advanced age, to suggest individual has an estimated life expectancy of less than 10 years; AND

c. Patient must fall into one of the following stages, as defined by the NCCN* (See Note 1):
   i. Low Risk
   ii. Favorable Intermediate Risk

2. The one-time use of Prolaris or Decipher is considered MEDICALLY NECESSARY in individuals with unfavorable intermediate- and high-risk disease, as defined by the NCCN (see Note 1) only if ALL of the following criteria have been met:

   a. Needle biopsy with localized adenocarcinoma of prostate with no clinical evidence of metastasis or lymph node involvement; AND

   b. No presence of significant co-morbidities, including advanced age, to suggest individual has an estimated life expectancy of less than 10 years

3. The following tests to assess and/or monitor prostate cancer are considered NOT MEDICALLY NECESSARY:

   a. Ki-67 immunohistochemistry

   b. PTEN loss

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

4. The following tests are EXPERIMENTAL AND INVESTIGATIONAL including but not limited to:

   a. Urine testing for gene expression profile and/or protein biomarkers to assess prostate cancer, including ExoDX Prostate (IntelliScore) and SelectMDx

   b. Prostate cancer gene 3 (PCA3) testing

   c. PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate-specific antigen]) ratio

   d. Gene hypermethylation testing to assess prostate cancer

   e. Proveri Prostate Cancer Assay (PPCA)

**NOTE 1:** NCCN Prostate Cancer Initial Risk Stratification and Staging Workup for Clinically Localized Disease (NCCN, 2020).

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Clinical/pathologic Features</th>
<th>Molecular/Biomarker Analysis of Tumor</th>
<th>Germline Testing</th>
</tr>
</thead>
</table>
| Very Low‡ | Has all of the following:  
• T1c; AND | Not indicated | Recommended if family history positive or |
<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Clinical/pathologic Features</th>
<th>Molecular/Biomarker Analysis of Tumor</th>
<th>Germline Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Has all of the following but does not qualify for very low risk:</td>
<td>Consider if life expectancy ≥10 y&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Recommended if family history positive or intraductal/cribriform histology</td>
</tr>
<tr>
<td>Favorable Intermediate&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Has all of the following:</td>
<td>Consider if life expectancy ≥10 y&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Recommended if family history positive or intraductal/cribriform histology</td>
</tr>
<tr>
<td>Unfavorable Intermediate&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Has one or more of the following:</td>
<td>Consider if life expectancy ≥10 y&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Recommended if family history positive or intraductal histology</td>
</tr>
<tr>
<td>High</td>
<td>Has no very-high-risk features and has at least one high-risk feature:</td>
<td>Consider if life expectancy ≥10 y&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Recommended</td>
</tr>
<tr>
<td>Very High</td>
<td>Has at least one of the following:</td>
<td>Not routinely recommended</td>
<td>Recommended</td>
</tr>
</tbody>
</table>

- **Molecular/Biomarker Analysis of Tumor**
  - Grade Group 1
  - PSA <10 ng/mL
  - Few than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core
  - PSA density <0.15 ng/mL/g
  - intraductal/cribriform histology

- **Germline Testing**
  - Consider if life expectancy ≥10 y<sup>e</sup>
  - Recommended if family history positive or intraductal/cribriform histology
  - Consider if life expectancy ≥10 y<sup>e</sup>
  - Recommended if family history positive or intraductal histology
  - Recommended
Grade Group 4 or 5

For asymptomatic patients, in very low, low, and intermediate risk groups with life expectancy ≤5 years, no imaging or treatment is indicated until the patient becomes symptomatic, at which time ADT should be given.

e. Men 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, Prolaris, and ProMark. Men 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 radical prostatectomy (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 progression after RP or external beam therapy, and likelihood of developing metastasis after RP or salvage radiotherapy.

Scientific Background

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 2020, the American Cancer Society estimates that approximately 191,930 new prostate cancer diagnoses and approximately 33,330 prostate cancer deaths will occur; although, the 5-year survival rate between 2007-2013 was 99%. About one man in nine will be diagnosed with prostate cancer during his lifetime in the United States (ACS, 2020; 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, 2020).

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, 2020). 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 prostate-specific antigen (PSA) assessment. The Gleason score is a scoring system used to categorize a prostate cancer biopsy based on risk assessment.

Hu et al. (2018) evaluated the utility of three genomic expression classifiers (GEC), including Decipher, Oncotype, and Prolaris. A total of 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 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 American Urological Association (AUA) risk category; it 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 been 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 the Cancer of the Prostate Risk Assessment (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. (2018) 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 recommends Decipher and Oncotype DX as other options for gene expression profiles (NCCN, 2020).

**Oncotype DX**

Oncotype DX is similar to Prolaris in that it assesses levels of gene expression, should be used for lower-risk patients, and can 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) 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, 2019a). 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).

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).”

Decipher

Decipher is a genomic prognostic test that is used to predict cancer outcomes in patients that have undergone a radical prostatectomy (RP), which is the removal of the prostate gland and surrounding tissues. Decipher 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, Löppenberg, Sood, Sammon, & Abdollah, 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.

ExoDX Prostate (IntelliScore)

ExoDX is a urinary test that detects the expression level of three genetic biomarkers (ERG, PCA3, and SPDEF) (AMA, 2019; ExoSome, 2019). 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).

McKiernan et al. (2016) used this test 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).

**ConfirmMDX**

ConfirmMDX uses methylation-specific polymerase chain reaction (PCR) to identify whether a patient with a previously negative prostate biopsy should undergo a repeat biopsy. This test identifies methylation of three genes (GSTP1, APC, and RASSF1) (MDx, 2018a). 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, 2018b). 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 SelectDX results on clinical decision making, and found that out of 253 patients that SelectDX evaluated as “negative,” only 12% underwent a biopsy (Shore, 2018).

**Proveri**

Proveri evaluates 114 diagnostic biomarkers and 15 prognostic biomarkers to assess prostate cancer. The diagnostic biomarkers were validated with 364 samples (243 tumor samples, 121 control) and assessed at a sensitivity of 88% and specificity of 98% (97% accuracy). The prognostic biomarkers were validated with 49 samples (40 relapse patients, 9 with indolent disease) and were calculated to have a sensitivity of 88%, a specificity of 80% and were 87% accurate (Proveri, 2013).

**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).

**ProMark**

Another test that may have utility is ProMark. It measures the levels of eight proteins through the quantitative immunofluorescence of a biopsy specimen. ProMark 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).

Finally, the NCCN specifically recommends against two particular tests in assessment of prostate cancer; Ki-67 staining and phosphatase and tensin homolog (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, D'Amico, & Freedland, 2019a). 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., 2019a).

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., 2019a). 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) (NCCN, 2019a, 2019b, 2020)

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, 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 and life expectancy ≥10 y may consider the use of the following tumor-based molecular assays: Decipher, Oncotype DX Prostate, Prolaris, and Promark. Men 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 radical prostatectomy (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 progression after radical prostatectomy or external beam therapy, and likelihood of developing metastasis after RP or external beam therapy, and likelihood of developing metastasis after RP or salvage radiotherapy (NCCN, 2020).” Furthermore, they note that clinicians may consider testing patients with regional prostate cancer for somatic mutations in DNA repair genes BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, and CDK12; “If mutations in BRCA2, BRCA1, ATM, CHEK2 or PALB2 are found, the patient should be referred for genetic counseling (NCCN, 2020).” The NCCN noted that somatic tumor testing of the aforementioned genes has 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, 2019b, 2020).

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, 2020):

<table>
<thead>
<tr>
<th>Test</th>
<th>Platform</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Decipher</strong></td>
<td>Whole-Transcriptome 1.4M RNA expression (44000 genes), oligonucleotide microarray optimized for FFPE tissue</td>
<td>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 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir)</td>
</tr>
<tr>
<td><strong>KI-67</strong></td>
<td>IHC</td>
<td>Not recommended</td>
</tr>
<tr>
<td><strong>Oncotype DX</strong></td>
<td>Quantitative RT-PCR for 12 prostate cancer-related genes and 5 housekeeping controls</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Prolaris</strong></td>
<td>Quantitative RT-PCR for 31 cell cycle-related genes and 15 housekeeping controls</td>
<td>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.</td>
</tr>
<tr>
<td><strong>ProMark</strong></td>
<td>Multiplex immunofluorescent staining of 8 proteins</td>
<td>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.</td>
</tr>
<tr>
<td><strong>PTEN</strong></td>
<td>Fluorescence in situ hybridization or IHC</td>
<td>Not recommended</td>
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</table>

The NCCN also acknowledged that ConfirmMDX 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, 2019b).

**American Association of Clinical Urologists Inc. (AACU) (AACU, 2018; LUGPA, 2018)**

The 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).

**American Society of Clinical Oncology (ASCO) (Bekelman et al., 2018; Eggener et al., 2019)**

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) (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 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).

In 2019, 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 (Eggener et al., 2019).”

**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) (EAU, 2018)**

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;
- 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) (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 22, 2020 (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 germ line \( BRCA1 \) and \( BRCA2 \) 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.

### Applicable CPT/HCPCS Procedure Codes

<table>
<thead>
<tr>
<th>Code Number</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0005U</td>
<td>Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score <strong>Proprietary test:</strong> ExosomeDx® Prostate (IntelliScore)</td>
</tr>
<tr>
<td>0047U</td>
<td>Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score <strong>Proprietary test:</strong> Oncotype DX® Genomic Prostate Score™</td>
</tr>
<tr>
<td>81313</td>
<td>PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)</td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>Code Number</td>
<td>Code Description</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>81541</td>
<td>Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score. Proprietary test: Prolaris®</td>
</tr>
<tr>
<td>81542</td>
<td>Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score. Proprietary test: Decipher® Prostate. Lab/Manufacturer: Biosciences.</td>
</tr>
<tr>
<td>81551</td>
<td>Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy. Proprietary test: ConfirmMDx®</td>
</tr>
</tbody>
</table>


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

### Evidence-based Scientific References


FDA. (2014). BRACANALYSIS CDX. *Summary of Safety and Effectiveness Data (SSED).* Retrieved from [https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140020B.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140020B.pdf)


### Policy Implementation/Update Information

**1/1/20** New Policy

**8/1/20** Literature review did necessitate following modification to the coverage criteria:

Addition of the following CC per NCCN v.1.2020: • The one-time use of Prolaris or Decipher MEDICALLY NECESSARY in individuals with unfavorable intermediate- and high-risk disease, as defined by the NCCN (see Note 1) only if ALL of the following criteria have been met: o Needle biopsy with localized adenocarcinoma of prostate with no clinical evidence of metastasis or lymph node involvement; AND o No presence of significant co-morbidities, including advanced age, to suggest individual has an estimated life expectancy of less than 10 years. Addition of the following wording “including but not limited to” to the last CC for clarity. Updated CC 1 to MEDICALLY NECESSARY if the list of criteria included are met.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.