Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedures addressed by this guideline</th>
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What are gene expression profiling tests for prostate cancer

Definition

Prostate cancer (PC) is the most common cancer and a leading cause of cancer-related deaths worldwide. It is considered a heterogeneous disease with highly variable prognosis.¹

- High-risk prostate cancer (PC) patients treated with radical prostatectomy (RP) undergo risk assessment to assess future disease prognosis and determine optimal treatment strategies. Post-RP pathology findings, such as disease stage, baseline Gleason score, time of biochemical recurrence (BCR) after RP, and PSA doubling-time, are considered strong predictors of disease-associated metastasis and mortality. Following RP, up to 50% of patients have pathology or clinical features that are considered at high risk of recurrence and these patients usually undergo post-RP treatments, including adjuvant or salvage therapy or radiation therapy, which can have serious risks and complications. According to clinical practice guideline recommendations, high risk patients should undergo 6 to 8 weeks of radiation therapy (RT) following RP. However, approximately 90% of high-risk patients do not develop metastases or die of prostate cancer, and instead may be appropriate candidates for alternative treatment approaches, including active surveillance (AS). As such, many patients may be subjected to unnecessary follow-up procedures and their associated complications, highlighting the need for improved methods of prognostic risk assessment.²,³

- Several genomic biomarkers have been commercially developed to augment the prognostic ability of currently available routine clinical and pathological tests and identify those patients most and least likely to benefit from a specific treatment strategy. Prognostic genomic tests, including gene expression profiling tests, may help to avoid overtreatment by reclassifying those men originally identified as high risk, but who are unlikely to develop metastatic disease. Genomic biomarkers may
also play a role in assisting clinicians to tailor personalized and more appropriate treatments for subgroups of PC patients, and improve overall health outcomes.\textsuperscript{2,3}

**Test information**

- Gene expression profiles (GEPs) evaluate the expression of several genes using one sample. Gene expression is determined through RNA analysis, using either reverse transcriptase (RT) polymerase chain reaction (PCR) or DNA microarrays.\textsuperscript{4}
- **Prolaris\textsuperscript{®} (Myriad\textsuperscript{®} Genetics)\textsuperscript{5}
  
  o According to the manufacturer, Prolaris is a genomic test developed to predict PC-specific mortality in PC patients after needle biopsy, as well as post-RP patients to assess the risk of BCR. This test is designed to assist clinicians with predicting tumor aggressiveness combined with clinical and pathologic variables (Gleason score, PSA).

**Guidelines and evidence**

**National Comprehensive Cancer Network**

- The National Comprehensive Cancer Network (NCCN) 2018 Clinical Practice Guidelines on Prostate Cancer state the following regarding molecular assays:\textsuperscript{6}
  
  o “Men with low or favorable intermediate risk disease may consider the use of the following tumor-based molecular assays: Decipher, Oncotype DX Prostate, Prolaris, Promark. Retrospective studies have shown that molecular assays performed on prostate biopsy or radical prostatectomy specimens provide prognostic information independent of NCCN risk groups.”
  
  o According to NCCN, the Molecular Diagnostic Services Program (MolDX) recommendations stated the following:\textsuperscript{6}
    
    - **Decipher:** “Cover post-RP for 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir)”
    
    - **Prolaris:** “Cover post-biopsy for NCCN very-low, low-risk, and favorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy.”
    
    - **Oncotype DX Prostate:** “Cover post-biopsy for NCCN very-low, low-risk, and favorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy.”
    
    - **ProMark:** “Cover post-biopsy for NCCN very-low and low-risk prostate cancer in patients with at least 10 years life expectancy who have not
received treatment for prostate cancer and are candidates for active surveillance or definitive therapy.”

- “These molecular biomarker tests have been developed with extensive industry support, guidance, and involvement, and have been marketed under the less rigorous FDA regulatory pathways for biomarkers. Although full assessment of their clinical utility requires prospective randomized clinical trials, which are unlikely to be done, the panel believes that men with low or favorable intermediate disease may consider the use of Decipher, Oncotype DX Prostate, Prolaris, or ProMark during initial risk stratification.”

**American Association of Clinical Urologists**

The American Association of Clinical Urologists has issued a position statement on genomic testing in prostate cancer that states the following:7

- “The AACU supports the use of tissue-based molecular testing as a component of risk stratification in prostate cancer treatment decision making.”

**American Urological Association, ASTRO, and the Society of Urologic Oncology**

The AUA/ASTRO/SUO guideline for clinically localized prostate cancer states the following:8

- “Among most low-risk localized prostate cancer patients, tissue based genomic biomarkers have not shown a clear role in the selection of candidates for active surveillance.”

**Prolaris**

**Prolaris Literature Review**9-21

- Clinical studies published by the manufacturer suggest that Prolaris may have potential prognostic value in patients with localized prostate cancer and following RP. However, it is not certain if use of Prolaris improves risk assessment information provided by conventional clinicopathologic variables, following conservative management or after surgery. It also remains uncertain if use of Prolaris in clinical practice leads to changes in clinically appropriate disease management strategies and subsequent improvement in patient-relevant health outcomes.

- Several limitations characterizing the evidence base weaken the strength of these findings. The available studies focused on primarily evaluating associations between results of Prolaris and the incidence of disease recurrence or mortality, which represents a preliminary stage of development of prognostic tests. The most appropriate clinical decisions to be made based on Prolaris test results have not been clearly established since there are no published studies that have reported the ability of the Prolaris test to prospectively predict patient-relevant health outcomes by virtue of prognostic risk assessment or changes made to treatment
recommendations. The evidence base may also be subject to publication bias. With one exception, the reviewed studies with consistently positive or favorable results were sponsored or funded by the test manufacturer. The single study not funded by the manufacturer, which examined the ability of Prolaris to predict tumor grade and stage following surgery, reported that 20 of 52 patients were misclassified by the Prolaris test (using clinicopathologic variables as the reference standard), suggesting that use of the test may be misleading in some cases.

• In some cases, study follow-up was very short, and may was not sufficiently long enough to capture metastatic event data, particularly among men with localized disease who have low rates of mortality. In addition, the total number of identified cases in each study was relatively small, which limits the generalizability of study results to a heterogeneous patient population usually observed in the real world.

Clinical Trials

Long-term Study to Evaluate and Clinical Outcomes in patients with Favorable Intermediate Risk Localized Prostate Cancer

• “This is a long-term prospective registry study to determine whether Prolaris testing in patients with favorable intermediate risk prostate cancer influences physician management decisions toward conservative treatment in patients with Prolaris low-risk scores without negatively impacting patient oncologic outcomes, thereby sparing low-risk patients from unnecessary treatments and associated side-effects.”
• NCT03290508
• Recruiting

Prospective Prolaris Value and Efficacy

• “This is a prospective study to measure the impact on first-line therapy of genomic testing of biopsy tissue from recently diagnosed treatment-naïve patients with early stage localized prostate cancer.”
• NCT03152448
• Recruiting

Criteria

• This test is considered investigational and/or experimental.
  o Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical
management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.

- In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

References


5. Prolaris website. Available at: [https://prolaris.com/](https://prolaris.com/)


