

Test Specific Guidelines





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Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
Prolaris	<u>81541</u>

What Are Gene Expression Profiling Tests for Prostate Cancer?

Definition

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

At the time of diagnosis of localized PC, patients typically undergo a prognostic risk assessment with routine clinical and pathological tests to assess the probability of subsequent progression or metastasis. These prognostic assessments help to identify lower risk patients with indolent disease who may opt for active surveillance (AS), or higher risk patients with more aggressive disease who may benefit from a treatment intervention.

High-risk prostate cancer (PC) patients treated with radical prostatectomy (RP) also 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 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}

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Several genomic biomarkers have been commercially developed to augment the prognostic ability of currently available routine clinical and pathological tests and identify those patients either at the time of diagnosis of localized PC or after radical prostatectomy (RP) 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.^{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.⁴

Prolaris[®] (Myriad[®] Genetics)⁵⁻⁹

According to the manufacturer, Prolaris is a genomic test developed to predict 10 year prostate cancer-specific mortality risk in patients after needle biopsy. This test is designed to assist clinicians with predicting tumor aggressiveness combined with clinical and pathologic variables (Gleason score, PSA).

The test is performed on formalin-fixed, paraffin-embedded tissue obtained from either prostate biopsy or surgically removed tissue. The expression of 31 cellcycle genes and 15 housekeeping genes is measured by quantitative reversetranscriptase-PCR and used to generate a Prolaris Score. A patient's Prolaris score is reported as a number between 1 and 10. Higher scores represent more aggressive disease, with each 1-unit increase representative of a doubling in risk

The Prolaris score is combined with the patient's Cancer of the Prostate Risk Assessment (CAPRA) score to generate the 10-year prostate cancer-specific mortality risk.

Guidelines and Evidence

American Association of Clinical Urologists

<u>The American Association of Clinical Urologists (AACU, 2018) has issued a</u> <u>position statement on genomic testing in prostate cancer that states the</u> <u>following:¹⁰</u>

"The AACU supports the use of tissue-based molecular testing as a component of risk stratification in prostate cancer treatment decision making. ... We also support ongoing research to further refine the prognostic power of these tests." American Society of Clinical Oncology

<u>The American Society of Clinical Oncology (ASCO, 2020) issued a guideline in</u> <u>molecular biomarkers in prostate cancer. This guideline states:¹¹</u>

<u>"Are there molecular biomarkers to diagnose clinically significant prostate cancer?"</u>

"Recommendation 2.1. 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 (Type: Evidence based; Evidence quality: Intermediate; Recommendation: Moderate)."

"Recommendation 2.2. 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 (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate)."

"Are there molecular biomarkers to guide the decision of postprostatectomy adjuvant versus salvage radiation?"

"Recommendation 3.1. 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 (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate)."

"Recommendation 3.2. 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 (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate)."

American Urological Association and American Society of Radiation Oncology

The American Urological Association and American Society for Radiation Oncology (AUA/ASTRO, 2022) published an evidence-based guideline on localized prostate cancer endorsed by the Society of Urologic Oncology (SGO) that stated:¹²

"Clinicians may selectively use tissue-based genomic biomarkers when added risk stratification may alter clinical decision-making. (Expert Opinion)"



<u>"Clinicians should not routinely use tissue-based genomic biomarkers for risk</u> stratification or clinical decision-making. (Moderate Recommendation; Evidence Level: Grade B)"

"Regarding tissue-based genomic biomarkers, several currently available commercial tests, including Prolaris, Oncotype Dx, and Decipher, variously offer prediction of adverse pathology as well as the risks of biochemical recurrence, metastasis, and prostate cancer death. However, most of the reported studies to date that evaluated the prognostic ability of these genomic tests did not meet inclusion criteria for the systematic review as the studies used surgical (ie, prostatectomy) rather than biopsy specimens."

National Comprehensive Cancer Network

<u>The National Comprehensive Cancer Network (NCCN, 2022) Clinical Practice</u> <u>Guidelines on Prostate Cancer state the following regarding molecular assays:¹³</u>

"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."

<u>"Retrospective studies have shown that tumor-based molecular assays</u> <u>performed on prostate biopsy or RP specimens provide prognostic information</u> <u>independent of NCCN or CAPRA risk groups. These include, but are not limited</u> <u>to, likelihood of death with conservative management, likelihood of biochemical</u> <u>progression after RP or EBRT [external beam radiation therapy], and likelihood of</u> <u>developing metastasis after RP or salvage radiotherapy."</u>

"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 and life expectancy greater than or equal to 10 years may consider the use of Decipher, Oncotype DX Prostate, or Prolaris during initial risk stratification."

Selected Relevant Publications

Overall, the evidence base for Prolaris consists primarily of retrospective clinical validity studies reporting on the strength of the association of Prolaris scores with biochemical recurrence or disease-specific mortality.¹⁴⁻³⁵ Several decision impact studies were identified that serve as surrogate studies for direct clinical utility evaluation. It remains unclear if the use of Prolaris in newly diagnosed patients leads to improvements in patient-important outcomes, such as morbidity, mortality, or quality of life.

Several ongoing clinical trials could provide meaningful insight upon their completion regarding these gaps in the evidence. Additional information can be found at https://clinicaltrials.gov.

<u>Criteria</u>

This test is considered investigational and/or experimental.

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.

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