Prolaris

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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.

Procedures addressed by this guideline	Procedure codes
Prolaris	81541

Criteria

Introduction

Requests for Prolaris testing are reviewed using the following criteria.

This test is considered Experimental, Investigational, or Unproven.

- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.
- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

What are gene expression profiling tests for prostate cancer?

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

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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]
- 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 cell-cycle genes and 15 housekeeping genes is measured by quantitative reverse-

transcriptase-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

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

- “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

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

- "Are there molecular biomarkers to diagnose clinically significant prostate cancer?"
    - "Recommendation 2.1. Commercially available molecular biomarkers (ie, Oncotype Dx Prostate [now Genomic Prostate Score], 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)"
- "Clinicians should not routinely use tissue-based genomic biomarkers for risk 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 [now Genomic Prostate Score], 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

The National Comprehensive Cancer Network (NCCN, 2025) Clinical Practice Guidelines on Prostate Cancer state the following regarding molecular assays:[13]

- "Retrospective case cohort studies have shown that these assays provide prognostic information independent of NCCN or CAPRA risk groups, which include likelihood of death with conservative management, likelihood of biochemical recurrence after radical prostatectomy or EBRT [external beam radiation therapy], likelihood of adverse pathologic features after radical prostatectomy, and likelihood of developing metastasis after operation, definitive EBRT, or post-recurrence EBRT."
- "These molecular biomarker tests have been developed with extensive industry support, guidance, and involvement, and have been marketed under the less rigorous U.S. Food and Drug Administration (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 [now Genomic Prostate Score], or Prolaris during initial risk stratification. Patients with unfavorable intermediate- and high-risk disease and life expectancy greater than or equal to 10 years may consider the use of Decipher or Prolaris."

- NCCN does not include Prolaris in its table of advanced molecular tools with evidence to support clinical use.

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.[14-45] 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. This conclusion is echoed by several systematic reviews.

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**.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Prolaris will ensure that members will not receive testing for which there is not a body of evidence demonstrating clinical utility and is therefore considered experimental, investigational, or unproven. Use of a test that does not have evidence to support clinical utility can lead to negative consequences. These include but are not limited to physical implications, psychological implications, treatment burden, social implications, and dissatisfaction with healthcare.[46] However, it is possible that there will be a delay in care while providers search for an appropriate test with sufficient evidence (analytical validity, clinical validity, and clinical utility).

References

1. Bostrom PJ, Bjartell AS, Catto JW, et al. Genomic Predictors of Outcome in Prostate Cancer. *Eur Urol.* Dec 2015;68(6):1033-1044.
2. Marrone M, Potosky AL, Penson D, Freedman AN. A 22 Gene-expression Assay, Decipher® (GenomeDx Biosciences) to Predict Five-year Risk of Metastatic Prostate Cancer in Men Treated with Radical Prostatectomy. *PLoS Curr.* Nov 17 2015;7.
3. Moschini M, Spahn M, Mattei A, Cheville J, Karnes RJ. Incorporation of tissue-based genomic biomarkers into localized prostate cancer clinics. *BMC Med.* Apr 04 2016;14:67.
4. AHRQ. Gene expression profiling for predicting outcomes in patients with stage II colon cancer. 2012.
5. Prolaris website. Available at: **https://myriad.com/genetic-tests/prolaris-patient/**
6. Myriad Genetics Inc. Prolaris Clinical Dossier. Available at: **https://s3.amazonaws.com/myriad-web/Managed+Care/Prolaris_ClinicalDossier-DigitalMagazine.pdf.**
7. Myriad Genetics Inc. Prolaris Test Report. Available at: **https://s3.amazonaws.com/myriad-web/Managed+Care/Prolaris-Test-Report-SAMPLE.pdf**.
8. Myriad Genetics Inc. Physician Central. Available at: **https://myriad.com/urology/providers/**

9. Myriad Genetics Inc. Prolaris executive summary . Available at: **https://s3.amazonaws.com/myriad-web/Managed+Care/Prolaris-Executive-Summary.pdf.**
10. American Association of Clinical Urologists, Inc. (AACU) website. Position statement: genomic testing in prostate cancer. Dated February 26, 2018. Available at: **https://aacuweb.org/wp-content/uploads/2022/02/Position-Statement-Tissue-based-genetic-testing-in-prostate-cancer-Endorsement-02-26-18.pdf**
11. Eggener SE, Rumble RB, Armstrong AJ, et al. Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline. *J Clin Oncol*. 2020;38(13):1474-1494. doi: 10.1200/JCO.19.02768
12. Eastham JA, Auffenberg GB, Barocas DA et al: Clinically localized prostate cancer: AUA/ASTRO guideline part I: introduction, risk assessment, staging and risk-based management. *J Urol*. 2022;208(1):10-18. doi: 10.1097/JU.0000000000002757.
13. Spratt DE, Schaeffer EM, Srinivas S, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2025 – April 16, 2025. Prostate Cancer. Available at: **https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate cancer V2.2025 – April 16, 2025. ©2025 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines®, go online to **NCCN.org**
14. Sommariva S, Tarricone R, Lazzeri M, et al. Prognostic value of the cell cycle progression score in patients with prostate cancer: A Systematic Review and Meta-analysis. *Eur Urol.* Jan 2016;69(1):107-115.
15. Cuzick J, Swanson GP, Fisher G, et al. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. *Lancet Oncol.* Mar 2011;12(3):245-255.
16. Cuzick J, Berney DM, Fisher G, et al. Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort. *Br J Cancer.* Mar 13 2012;106(6):1095-1099.
17. Cooperberg MR, Simko JP, Cowan JE, et al. Validation of a cell-cycle progression gene panel to improve risk stratification in a contemporary prostatectomy cohort. *J Clin Oncol.* Apr 10 2013;31(11):1428-1434.
18. Freedland SJ, Gerber L, Reid J, et al. Prognostic utility of cell cycle progression score in men with prostate cancer after primary external beam radiation therapy. *Int J Radiat Onocol Biol Phys.* Aug 1 2013;86(5):848-853.
19. Crawford ED, Scholz MC, Kar AJ, et al. Cell cycle progression score and treatment decisions in prostate cancer: results from an ongoing registry. *Curr Med Res Opin.* Jun 2014;30(6):1025-1031.
20. Shore N, Concepcion R, Saltzstein D, et al. Clinical utility of a biopsy-based cell cycle gene expression assay in localized prostate cancer. *Curr Med Res Opin.* Apr 2014;30(4):547-553.
21. Cuzick J, Stone S, Fisher G, et al. Validation of an RNA cell cycle progression score for predicting death from prostate cancer in a conservatively managed needle biopsy cohort. *Br J Cancer.* Jul 28 2015;113(3):382-389.
22. Oderda M, Cozzi G, Daniele L, et al. Cell-cycle progression-score might improve the current risk assessment in newly diagnosed prostate cancer patients. *Urology.* 2017;102:73-78.
23. Shore ND, Kella N, Moran B, et al. Impact of the cell cycle progression test on physician and patient treatment selection for localized prostate cancer. *J Urol.* Mar 2016;195(3):612-618.
24. Lin DW, Crawford ED, Keane T, et al. Identification of men with low-risk biopsy-confirmed prostate cancer as candidates for active surveillance. *Urol Oncol*. 2018;36(6):310.e317-310.e313.
25. Rayford W, Greenberger M, Bradley RV. Improving risk stratification in a community-based African American population using cell cycle progression score. *Transl Androl Urol*. 2018;7(Suppl 4):S384-s391.
26. Canter DJ, Reid J, Latsis M, et al. Comparison of the prognostic utility of the cell cycle progression score for predicting clinical outcomes in African American and Non-African American Men with localized prostate cancer. *Eur Urol*. 2018.
27. Kaul S, Wojno KJ, Stone S, et al. Clinical outcomes in men with prostate cancer who selected active surveillance using a clinical cell cycle risk score. *Per Med*. 2019;16(6):491-499.
28. Hu JC, Tosoian JJ, Qi J, et al. Clinical utility of gene expression classifiers in men with newly diagnosed prostate cancer. *JCO Precis Oncol*. 2018(2):1-15.
29. Tosoian JJ, Chappidi MR, Bishoff JT, et al. Prognostic utility of biopsy-derived cell cycle progression score in patients with National Comprehensive Cancer Network low-risk prostate cancer undergoing radical prostatectomy: implications for treatment guidance. *BJU Int*. 2017;120(6):808-814.

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30. Canter DJ, Freedland S, Rajamani S, et al. Analysis of the prognostic utility of the cell cycle progression (CCP) score generated from needle biopsy in men treated with definitive therapy. *Prostate Cancer Prostatic Dis*. 2019;23(1):102-107. doi: 10.1038/s41391-019-0159-9
31. Creed JH, Berglund AE, Rounbehler RJ, et al. Commercial gene expression tests for prostate cancer prognosis provide paradoxical estimates of race-specific risk. *Cancer Epidemiol Biomarkers Prev*. 2020;29(1):246-253. doi: 10.1158/1055-9965.epi-19-0407
32. Morris DS, Woods JS, Edwards B, et al. Prognostic capabilities and clinical utility of Cell Cycle Progression testing, Prostate Imaging Reporting And Data System, version 2, and clinicopathologic data in management of localized prostate cancer. *Urol Oncol*. 2020;S1078-1439(20):30604-30609. doi: 10.1016/j.urolonc.2020.11.016
33. Cooperberg MR, Cowan JE, Lindquist KJ, et al. Multiple tissue biomarkers independently and additively predict prostate cancer pathology outcomes. *Eur Urol*. 2021;79(1):141-149. doi: 10.1016/j.eururo.2020.09.003
34. Lehto TPK, Sturenberg C, Malén A, et al. Transcript analysis of commercial prostate cancer risk stratification panels in hard-to-predict grade group 2–4 prostate cancers. *The Prostate*. 2021;81(7):368-376. doi: 10.1002/pros.24108
35. Tward J, Lenz L, Flake DD, et al. The clinical cell-cycle risk (CCR) score is associated with metastasis after radiation therapy and provides guidance on when to forgo combined androgen deprivation therapy with dose-escalated radiation. *Int J Radiat Oncol Biol Phys*. 2022;113(1):66-76. doi: 10.1016/j.ijrobp.2021.09.034
36. Trock BJ, Jing Y, Mabey B, et al. Cell cycle progression score, but not phosphatase and tensin homolog loss, is an independent prognostic factor for metastasis in intermediate- and high-risk prostate cancer in men treated with and without salvage radiotherapy. *J Urol*. 2022;208(6):1182-1193. doi: 10.1097/ju.0000000000002922
37. Cuzick JM, Stone S, Lenz L, et al. Validation of the cell cycle progression score to differentiate indolent from aggressive prostate cancer in men diagnosed through transurethral resection of the prostate biopsy. *Cancer Reports*. 2021. doi: 10.1002/cnr2.1535
38. Hutten RJ, Odei B, Johnson SB, et al. Validation of the combined Clinical Cell-Cycle risk score to prognosticate early prostate cancer metastasis from biopsy specimens and comparison with other routinely used risk classifiers. *JCO Precis Oncol*. 2024;8:e2300364. doi: 10.1200/po.23.00364
39. Braun AE, Chan JM, Neuhaus J, et al. The impact of genomic biomarkers on a clinical risk prediction model for upgrading/upstaging among men with favorable-risk prostate cancer. *Cancer*. 2024;130(10):1766-1772. doi: 10.1002/cncr.35215
40. Spohn SKB, Draulans C, Kishan AU, et al. Genomic classifiers in personalized prostate cancer radiation therapy approaches: A systematic review and future perspectives based on international consensus. *Int J Radiat Oncol Biol Phys*. 2023;116(3):503-520. doi: 10.1016/j.ijrobp.2022.12.038
41. Boyer MJ, Carpenter D, Gingrich JR, et al. Prognostic value of genomic classifier testing for prostate cancer: A systematic review In: VA Evidence-based Synthesis Program Reports. Washington (DC): Department of Veterans Affairs (US); 2023: **https://www.ncbi.nlm.nih.gov/books/NBK594816/**
42. Boyer MJ, Carpenter DJ, Gingrich JR, et al. Genomic classifiers and prognosis of localized prostate cancer: A systematic review. *Prostate Cancer Prostatic Dis*. 2024. doi: 10.1038/s41391-023-00766-z
43. Tabriz AA, Boyer MJ, Gordon AM, et al. Impact of Genomic Classifiers on Risk Stratification and Treatment Intensity in Patients With Localized Prostate Cancer: A Systematic Review. *Ann Intern Med*. 2025;178(2):218-228. doi: 10.7326/ANNALS-24-00700
44. Roidos C, Anastasiadis A, Tsiakaras S, et al. Integration of Genomic Tests in Prostate Cancer Care: Implications for Clinical Practice and Patient Outcomes. *Curr Issues Mol Biol*. 2024;46(12):14408-14421. doi: 10.3390/cimb46120864
45. Sood A, Kishan AU, Evans CP, et al. The impact of positron emission tomography imaging and tumor molecular profiling on risk stratification, treatment choice, and oncological outcomes of patients with primary or relapsed prostate cancer: An international collaborative review of the existing literature. *Eur Urol Oncol*. 2024;7(1):27-43. doi: 10.1016/j.euo.2023.06.002
46. Korenstein D, Chimonas S, Barrow B, et al. Development of a conceptual map of negative consequences for patients of overuse of medical tests and treatments. *JAMA Inter Med*. 2018;178(10):1401-1407.

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