MEDICAL POLICY

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MEDICAL POLICY DETAILS	
Medical Policy Title	**Gene Expression Analysis for Prostate Cancer Management**
Policy Number	**2.02.48**
Category	**Technology Assessment**
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Archive Review Date	**N/A**
Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.* • *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.* • *If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.* • *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.*

POLICY STATEMENT

I. Based upon our criteria and assessment of the peer-reviewed literature, gene expression analysis to guide the management of prostate cancer, using the Oncotype DX Genomic Prostate Score (Oncotype DX Prostate), Prolaris, Decipher Prostate Cancer Classifier (Decipher), or ProMark assay during initial risk stratification is considered **medically appropriate** in patients who have a prostate and **BOTH** of the following:
   A. Low- or favorable intermediate-risk disease; AND
   B. Life expectancy of 10 or more years.

II. Based upon our criteria and assessment of the peer-reviewed literature, gene expression analysis to guide the management of prostate cancer, using the Prolaris or Decipher assay during initial risk stratification, is considered **medically appropriate** in in patients who have a prostate and **BOTH** of the following:
   A. Unfavorable intermediate- and high-risk disease; AND
   B. Life expectancy of 10 or more years.

III. Based upon our criteria and assessment of the peer-reviewed literature, gene expression analysis, with tests other than those listed above, is considered **not medically necessary.**

Refer to Corporate Medical Policy #10.01.05 Prostate Cancer Screening, Detection and Monitoring.

POLICY GUIDELINES

The Oncotype DX Prostate, Prolaris, and Decipher assays have been cleared for marketing by the U. S. Food and Drug Administration (FDA). Each is available under the auspices of the Clinical Laboratory Improvement Act (CLIA). Clinical laboratories may develop and validate tests in-house (laboratory-based tests (LDTs)) and market them as a laboratory service. LDTs must meet the general regulatory standards of the CLIA. Laboratories that offer LDTs must be licensed under the CLIA for high-complexity testing.

DESCRIPTION

Prostate cancer is the second most common cancer in the United States with a five-year overall survival of nearly 100% because most prostate cancer diagnosed is a localized disease. Treatment for prostate cancer may include radical prostatectomy, radiation therapy, androgen deprivation therapy, or a combination of any of these treatment options. Research shows that prostate cancer specific mortality is low, with indolent disease often going undiagnosed in patients who die of other causes. Individuals with newly diagnosed prostate cancer can have either aggressive or indolent forms of the disease, and current tools are unable to discriminate between the two. Consequently, all patients are treated as though they have aggressive disease, which leads to overtreatment. The United States Preventative Services Task Force (USPSTF) has recommended against widespread prostate-specific antigen (PSA) screening for prostate cancer because the prevalence of overtreatment harms more patients than it benefits. The American Urological Association (AUA) has taken a similar position, partially aligning with the USPSTF. Better options are needed to stratify patients and to confirm the type of prostate cancer so that patients with aggressive disease receive treatment, while those with a more indolent disease may be treated more conservatively and may benefit from active surveillance.

Gene expression assays have been developed to address this issue: the Oncotype DX for prostate cancer (Genomic Health, Redwood City, CA), the Prolaris (Myriad Genetics, Salt Lake City, UT), and the Decipher Prostate Cancer Classifier (Decipher), and ProMark assay.

The Oncotype DX prostate test is a multigene reverse transcription polymerase chain reaction (RT-PCR) assay designed to analyze underlying tumor biology in tumor tissue from diagnostic formalin-fixed parafilm-embedded (FFPE) core needle biopsies. The test includes five reference genes and 12 cancer genes representing distinct biological pathways with a known role in prostate tumorigenesis. Reference gene normalization is used to control for sources of pre-analytical and analytical variability, as well as to allow for variable RNA inputs. The Genomic Prostate Score (GPS) is calculated from the reference normalized expression of the 12 cancer-related genes. The GPS score ranges from 0 to 100 with the higher score reflecting a higher risk.

The Prolaris test is a gene expression-based assay that directly measures tumor cell growth characteristics in 31 genes related to cell cycle progression (CCP) and 15 housekeeping genes. A CCP score is determined which is used to predict 10-year prostate cancer specific disease progression and mortality. CCP scores range from -3.0 to 7.0 with the higher score indicating higher estimated 10-year prostate cancer risk.

The Decipher Prostate RP test predicts the probability of metastasis after surgery and provides an independent assessment of tumor aggressiveness with information distinct from that provided by Gleason score or PSA. The Decipher Prostate RP test uses the expression of 2 RNA biomarkers involved in multiple biological pathways across the genome that are associated with aggressive prostate cancer to calculate the probability of clinical metastasis within five years of radical prostatectomy surgery.

The Decipher Prostate Biopsy test, which is a whole transcriptome test, utilizes 22 coding and non-coding biomarkers that span seven cancer pathways, to provide a more accurate, independent prediction of risk and to assist physicians in determining whether the patient should undergo active surveillance, local therapy alone, or multi-modal therapy.

In 2014, the International Society of Urological Pathology (ISUP) Consensus developed a new system that assigned grade groups from 1 to 5, derived from the Gleason score. The lower the Gleason Score, the lower the Gleason grade with a Gleason score of 6 or less defining Grade 1. Grade 5 included a Gleason score of nine to 10.

Risk Group	Stage	Gleason Grade	PSA (ng/ml)	PSA density (ng/ml/g)	Other
Very Low	T1c	1	Less than 10	Less than 0.15	Fewer than three prostate biopsy fragments/cores positive, 50% or less cancer in any fragment/core
Low	T1-T2a	1	Less than 10		
Intermediate - favorable	T2b-T2c	2 or 3	10 to 20		50% or less biopsy cores positive
Intermediate-unfavorable	T2b-T2c	3	10 to 20		50% or more biopsy cores positive
High	T3a	4 or 5	Greater than 20		
Very High	T3b – T4	5			Greater than 4 cores with Grade Group 4 or 5

Per National Comprehensive Cancer Network (NCCN) (2022), life expectancy estimation is critical to informed decision-making in prostate cancer early detection and treatment. Estimation of life expectancy is possible for groups of patients but challenging for individuals. One tool to estimate life expectancy is the Social Security Administration tables found at: www.ssa.gov/OACT/STATS/table4c6.html

Risk stratification per 2022 NCCN Guidelines incorporates stage, Gleason grade, and PSA to assign patients to risk groups. The risk groups are used to select the appropriate options that should be considered and to predict the probability of biochemical recurrence after definitive local therapy.

RATIONALE

Analytical validity of the Oncotype DX Prostate assay was reported by Knezevic et al. (2013). The research showed that the assay could accurately measure expression of the 12 cancer-related and five reference genes over a range of absolute RNA inputs (0.005-320 ng) with a detection limit of 0.05 ng/ml. The analytic accuracy showed average variation of less than 9.7% across all samples at RNA inputs typical of needle biopsy specimens. The amplification efficiency for the 17 genes in the test ranged from 88% to 100%, with a median of 93% (SD=6%) for all 17 genes in the assay. Analytic precision was assessed by examining variability between replicate results obtained using the same messenger RNA (mRNA) input. Reproducibility was measured by calculating both within and between mRNA input variation. A low input level of 5 ng mRNA was used to reflect the lowest 2.5 percentile of a tumor sample of 0.023 cm^3. When converted to GPS units (unit measure for reporting test results), the standard deviation for analytic precision was 1.86 GPS units (95% confidence interval [CI], 1.60 to 2.20) on the 100-unit scale. The standard deviation for reproducibility was 2.11 GPS units (95% CI, 1.83 to 2.50) on the 100-point scale.

Analytical validity for the Prolaris test has yet to be specifically identified in the literature but has been suggested by studies on the performance of the TaqMan array platform which is used in the Oncotype DX Prostate and Prolaris tests.

Klein et al. (2014) suggested that incorporation of GPS into the analysis would be expected to lead to the treatment of fewer patients who have favorable pathology at prostatectomy, without increasing the number of patients with adverse pathology left untreated. However, in this study, all patients received a radical prostatectomy within six months of

diagnostic biopsy. No studies have been identified that address GPS in clinical practice and the manner in which treatment decisions were changed based on the score.

Two studies reported on the potential impact of the Prolaris CCP score on physician's treatment plans. In up to 33% of the cohort studied, treatment might, have or would have changed. The authors of both studies suggested that physicians perceive the CCP signature as clinically useful and would likely use it to justify use of more conservative management options such as active surveillance. However, patient preference was not factored in to either of the studies.

No studies have directly assessed the clinical validity of either the Oncotype DX Prostate or the Prolaris test.

The evidence for the Decipher assay in patients who have high-risk prostate cancer after radical prostatectomy includes one study of analytic validity; eight studies using archived samples; seven prospective-retrospective designs; one case-control) examining clinical validity; six decision curve analyses examining indirect evidence for clinical utility; and one prospective decision impact study. Relevant outcomes included overall survival, disease-specific survival, test accuracy, test validity, quality of life, and treatment-related morbidity. The clinical validity of the Decipher assay has been evaluated in samples of patients with high-risk prostate cancer who are undergoing different interventions following radical prostatectomy. Studies reported some incremental improvement in discrimination. However, it is unclear whether there is consistent improved reclassification—particularly to higher risk categories—or whether the test could be used to predict which patients will benefit from radiotherapy.

The Active Surveillance (AS) for the Management of Localized Prostate Cancer (Cancer Care Ontario Guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement (2016) stated that the use of ancillary tests beyond digital rectal exam (DRE), PRE, PSA, and biopsy to improve patient selection or as part of monitoring in an Active Surveillance regimen remains investigational. The AS protocol may include ancillary tests that are still under investigation. These could include multiparametric MRI (mpMRI) and/or genomic testing. mpMRI and genomic testing may be indicated when a patient's clinical findings are discordant with the pathologic findings and could be useful in identifying occult cancers or changes indicative of tumor progression in patients at risk. These tests may be helpful when the decision regarding active surveillance versus active treatment is uncertain (e.g., in cases of low-volume Gleason 3 + 4). mpMRI should not be used as a replacement for re-biopsy.

2022 National Comprehensive Cancer Network (NCCN) clinical practice guidelines for prostate cancer state that Decipher, Oncotype DX Prostate and Prolaris molecular assays may be considered in men with low or favorable intermediate risk prostate cancer and a life expectancy greater than or equal to ten years to help guide decision-making on treatment. Patients with unfavorable intermediate and high-risk disease may consider the use of Decipher and Prolaris molecular assays. Further, the Decipher test is recommended to inform adjuvant therapy when adverse features are found post prostatectomy and can be part of the discussion of risk stratification in patients with prostate specific antigen resistance/recurrence after radical prostatectomy (category 2B evidence).

In the Tumor Multigene Molecular Testing discussion section of the 2022 NCCN Guidelines they state "These molecular biomarker tests have been developed with extensive industry support, guidance, and involvement, and have been marketed under the less rigorous FDA regulatory pathway for biomarkers. Although full assessment of their clinical utility requires prospective randomized clinical trials, which are unlikely to be done, the panel believes that patients 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. 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. In addition, Decipher may be considered to inform adjuvant treatment if adverse features are found after radical prostatectomy and during workup for radical prostatectomy PSA persistence or recurrence (category 2B for the latter setting). Future comparative effectiveness research may allow these tests and others like them to gain additional evidence regarding their utility for better risk stratification of patients with prostate cancer"

Eggener et al. (2019), as part of an American Society of Clinical Oncology (ASCO) Multidisciplinary Expert Panel, conducted a systematic literature review of localized prostate cancer biomarker studies between Jan 2013 and 2019. Guidelines with recommendations for available tissue-based prostate cancer biomarkers were developed with a focus on patient selection for active surveillance, identification of clinically significant disease, choice of postprostatectomy

adjuvant or salvage radiation therapy (RT), and the value of tissue biomarkers compared to magnetic resonance imaging (MRI). Numerous molecular biomarkers have been developed to improve risk stratification and patient management. Few panels have undergone extensive validation; however, five are commercially available and have been shown in retrospective analyses to provide additional information beyond standard clinical models in prognostication or patient selection for therapy. The authors indicated that, while these tissue-based tests may improve risk stratification when added to standard clinical parameters, their use may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Examples included select patients with high-volume low-risk or favorable intermediate-risk prostate cancer considering active surveillance, and patients with high-risk features for treatment intensification. The authors also noted that, while testing may influence management decisions, there is no high-level evidence to indicate that the results from these panels improve quality of life or cancer-specific outcomes. There have been additional biomarkers evaluated that do not have sufficient data to be clinically actionable or that are not commercially available. Continued investigation of tissue-based molecular biomarkers in the context of clinical trials was recommended.

In summary the ASCO guideline for Molecular Biomarkers in Localized Prostate Cancer is as follows:

- In patients with prostate cancer who are most likely to benefit from active surveillance: Commercially available molecular biomarkers (Oncotype Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situation in which the assay results, when considered as a whole with routine clinical factors, is likely to affect management. (Type: Evidence based; Evidence quality: Intermediate; Recommendation: Moderate))
- To diagnose clinically significant prostate cancer: 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 was not recommended (Type: Evidence based; Evidence quality: Intermediate; Recommendation: Moderate)
- To guide the decision for adjuvant or salvage radiation postprostatectomy: The Expert Panel recommends consideration of a commercially available molecular biomarker (e.g., Decipher) may be offered 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).
- Comparative strengths and weaknesses of genomics or MRI in identifying clinically significant prostate cancer: In patients with newly diagnosed prostate cancer who are eligible for active surveillance, both MRI and genomics are intended to identify clinically significant cancers. Their use is endorsed only in situations in which the result, when considered with routine clinical factors, is likely to affect management. This may include, for instance, the initial management of patients who are potentially eligible for active surveillance, where 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 (Type: Informal consensus; benefits/harms ratio unknown; Evidence quality: Low; Strength of recommendation: Weak).

The authors concluded that there was insufficient evidence to recommend the routine use of these tests. The costs of testing and downstream therapy implications are considerable and currently not justified for routine use, financially or oncologically, based on available evidence. The tissue-based tests may improve risk stratification; however, their use is recommended only in situations in which a specific assay result, when considered in combination with routine clinical factors, will clearly affect the management. These assays have not been prospectively tested; nor have they been shown to improve intermediate or long-term outcomes, such as quality of life, need for treatment or survival. Rigorous and prospective clinical testing is warranted and strongly encouraged. Although the routine use of molecular biomarkers is not recommended, the Expert Panel recognized that there may be scenarios in which the biomarkers may be helpful to inform prognostication or to guide management decisions. Patients who are considering active surveillance of newly diagnosed prostate cancer with higher-risk features for progression, or patients who are struggling to determine whether adjuvant

versus early salvage postprostatectomy radiation therapy is most appropriate, may benefit from the biomarker information, added to the clinical factors, in determining the final treatment decisions.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

CPT Codes

Code	Description
81541	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 (Prolaris® Assay)
81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score (Decipher Prostate Cancer Assay)
81551	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 (Confirm MDx, MDx Health)
0047U	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 (Oncotype Dx Prostate Cancer Assay)
0005U **(E/I)**	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score (ExosomeDx® Prostate (IntelliScore), Exosome Diagnostics, Inc)
0359U **(E/I)**	Oncology (prostate cancer), analysis of all prostate-specific antigen (PSA) structural isoforms by phase separation and immunoassay, plasma, algorithm reports risk of cancer (*Effective date 01/01/2023*)
0403U **(E/I)**	Oncology (prostate), mRNA, gene expression profiling of 18 genes, first-catch post-digital rectal examination urine (or processed first-catch urine), algorithm reported as percentage of likelihood of detecting clinically significant prostate cancer. (MyProstateScore 2.0, LynxDx) *(effective 10/01/2023)*

HCPCS Codes

Code	Description
None	

ICD10 Codes

Code	Description
C61	Malignant neoplasm of prostate

Code	Description
D07.5	Carcinoma in situ of prostate
D29.1	Benign neoplasm of prostate
D40.0	Neoplasm of uncertain behavior of prostate
Z12.5	Encounter for screening for malignant neoplasm of prostate
Z85.46	Personal history of malignant neoplasm of prostate

REFERENCES

Alford AV, et al. The use of biomarkers in prostate cancer screening and treatment. Rev Urol 2017;19(4):221-234.

Brooks MA, et al. GPS assay association with long-term cancer outcomes: twenty-year risk of distant metastasis and prostate cancer-specific mortality. JCO Precision Oncol 2021 Feb;5:442-449

Canfield S, et al. Active surveillance use among a low-risk prostate cancer population in a large US payer system: 17-gene genomic prostate score versus other risk stratification methods. Rev Urol 2017;19(4):203-212.

Cucchiara V, et al. Genomic markers in prostate cancer decision making. Eur Urol 2018 Apr;73(4):572-582.

Dess RT and Spratt DE. Why the UK should consider gene expression testing in prostate cancer. Clin Oncol (R Coll Radiol) 2020 Mar;32(3):149-155.

*Eggener SE, et al. Molecular biomarkers in localized prostate cancer: ASCO Guideline. J Clin Oncol 2020 May a;38(13):1274-1494.

Eure G, et al. Use of a 17-gene prognostic assay in contemporary urologic practice: results of interim analysis in an observational cohort. Urology 2017 Sep;107:67-75.

Fine ND, et al. Genomic classifiers for treatment selection in newly diagnosed prostate cancer. BJU Int 2019 May 4 [Epub ahead of print].

Karnes RJ, et al. Validation of a genomic risk classifier to predict prostate cancer-specific mortality in men with adverse pathologic features. Eur Urol. 2018 Feb;73(2):168-175.

*Knezevic D, et al. Analytical validation of the Oncotype DX prostate cancer assay – a clinical RT-PCR assay optimized for prostate needle biopsies. BMC Genomics 2013;14:690.

Lamy PJ, et al. Prognostic biomarkers used for localized prostate cancer management: a systematic review. Eur Urol Focus. 2018 Dec;4(6):790-803.

Leapman MS, et al. Association between a 17-gene genomic prostate score and multiparametric prostate MRI in men with low and intermediate risk prostate cancer (PCa). PLoS One 2017 Oct 10;12(10):e0185535.

Lin DW, et al. 17-gene genomic prostate score test results in the Canary Prostate Active Surveillance Study (PASS) cohort. J Clin Oncol 2020 May 10;38(14):1549-1557.

Loeb S and Ross AE. Genomic testing for localized prostate cancer: where do we go from here? Curr Opinion Urol 2017 Sep:27(5):495-499.

Martin DT, et al. Prostate cancer genomic classifier relates more strongly to Gleason grade group than prostate imaging reporting and data system score in multiparametric prostate magnetic resonance imaging-ultrasound fusion targeted biopsies. Am J Roent 2019 Jun;212(6):1244-1252.

Na R, et al. Clinically available RNA profiling tests of prostate tumors: utility and comparison. Asian J Androl 2016 Jul-Aug;18(4):575-9.

*National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Prostate Cancer. V.4.2022. [https://www.nccn.org/professionals/physician_gls/pdf/prostate_blocks.pdf] accessed 1/06/23.

Nguyen PL, et al. Ability of a genomic classifier to predict metastasis and prostate cancer-specific mortality after radiation or surgery based on needle biopsy specimens. Eur Urol 2017 Nov;72(5):845-852.

Rayford W, et al. Improving risk stratification in a community-based African American population using cell cycle progression score. Transl Androl Urol 2018;7(Supp 4):S384-S391.

Salmasi A, et al. A 17-gene genomic prostate score assay provides independent information on adverse pathology in the setting of combined multiparametric magnetic resonance imaging fusion targeted and systematic prostate biopsy. J Urol 2018; 200: 564-572.

*Key Article

KEY WORDS

Prolaris®, Oncotype DX® Prostate, Confirm MDX®, Gene expression analysis for the prostate.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a no National Coverage Determination (NCD) or Local Coverage Determination (LCD) for gene expression analysis for prostate cancer management.

There is currently a Local Coverage Determination (LCD) for MolDX: Prostate Cancer Genomic Classifier Assay for Men with Localized Disease. Please refer to the following LCD website for Medicare members: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?LCDId=38339

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures. Please refer to the following LCD website for Medicare members: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ver=133&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=Active&bc=AggAAAIAgAAA&