MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**GENE EXPRESSION ANALYSIS FOR PROSTATE CANCER MANAGEMENT**
Policy Number	**2.02.48**
Category	**Technology Assessment**
Effective Date	**08/20/15**
Revised Date	**12/15/16, 02/15/18, 12/20/18**
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 product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.* • *If a Medicare 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.*

POLICY STATEMENT

Based on our criteria and assessment of the peer-reviewed literature, all gene expression analyses (e.g., Oncotype DX® Genomic Prostate Score, the Prolaris® Assay, ~~or~~ the Confirm MDx®Assay, or Decipher® Prostate Cancer Classifier Assay) to guide management of prostate cancer are considered **investigational**.

POLICY GUIDELINES

I.   Neither Prolaris® Assay, Oncotype DX® Genomic Prostate Score, Confirm MDx® *Assay*, or Decipher® Prostate Cancer Classifier Assay is cleared for marketing by the U. S. Food and Drug Administration. 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 by CLIA for high-complexity testing.

II.   The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

DESCRIPTION

Prostate cancer is the second most common cancer in the United States with a 5 year overall survival of nearly 100% because the vast majority of prostate cancer diagnosed is localized disease. Treatment for prostate cancer may include radical prostatectomy, radiation therapy, androgen deprivation therapy, or a combination of any of these treatment options. It has been shown that prostate cancer specific mortality is low with indolent disease often going undiagnosed in men who die of other causes. Men 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 men are treated as though they have aggressive disease which leads to overtreatment. The 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 a similar statement to partially align 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.

Three tests have been developed to address this issue and include the Oncotype DX® for prostate cancer (Genomic Health, Redwood City, CA) and the Prolaris® (Myriad Genetics, Salt Lake City, UT) and the ConfirmMDx® (MDx Health, Irvine, CA) . The Oncotype DX® test is a multigene 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 5 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 allow for variable RNA inputs. The Genomic Prostate Score (GPS) is calculated from the reference normalized expression of the 12 cancer-related genes. Oncotype DX® is different from other Oncotype DX assays such as the Oncotype DX® for the breast because RNA input levels are 110-180 fold less. 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 and 15 housekeeping genes. A cell cycle progression (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. ConfirmMDx® assesses the methylation status of 3 biomarkers (GSTP1, RASSF1, APC) associated with prostate cancer. ConfirmMDx is intended for use in patients with high-risk factors such as elevated/rising prostate-specific antigen (PSA) or abnormal digital rectal examination (DRE), with a negative or non-malignant abnormal histopathology finding (e.g., atypical cell or high grade prostate intraepithelial neoplasia (HGPIN)) in the previous biopsy, and is being considered for repeat biopsy. The Decipher® 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 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 5 years of radical prostatectomy surgery.

RATIONALE

Analytical validity of the Oncotype DX® assay was reported by Knezevic et al (2013) that showed the assay could accurately measure expression of the 12 cancer-related and 5 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 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 both of these tests.

Klein et al., (2014) suggested incorporation of GPS would be expected to lead to fewer treatments of 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 6 months of diagnostic biopsy. No studies have been identified which address GPS in clinical practice and how 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. Treatment might have potentially changed or definitely would have changed in up to 33% of the cohort studied. The authors of both studies suggest 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 test.

The evidence for the Decipher® prostate cancer classifier in patients who have high-risk prostate cancer post radical prostatectomy includes 1 study of analytic validity, 8 studies using archived samples (7 prospective-retrospective designs, 1 case-control) examining clinical validity, and 6 decision curve analyses examining indirect evidence for clinical utility,

and 1 prospective decision im pact study. Relevant outcomes include overall survival, disease-specific survival, test accuracy, test validity, quality of life, and treatment-related morbidity. The clinical validity of the Decipher® genomic classifier has been evaluated in samples of patients with high-risk prostate cancer 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 men will benefit from radiotherapy.

A 2013 Blue Cross Blue Shield TEC Assessment of gene expression analysis for prostate cancer management assessed the incremental value of gene expression tests for discriminating men with aggressive and indolent disease to guide treatment decisions that improve net health outcomes. The Assessment concluded there was no evidence available on the clinical utility of either test for any clinical end point. There was insufficient evidence to determine whether Prolaris® or Oncotype Dx® Prostate testing affects the net health outcome, or to determine if the incremental value of either Prolaris® or Oncotype Dx® Prostate gene expression test compared with clinical criteria for discriminating men with aggressive and indolent disease to guide treatment decisions that improve the net health outcome, or to determine whether Prolaris® or Oncotype Dx® Prostate testing improves health outcomes in the investigational setting. TEC criteria were not met for either the Prolaris® or the Oncotype Dx® Prostate gene expression test.

The National Comprehensive Cancer Network NCCN (2018) include in their guidelines for prostate cancer tumor-based molecular assays which to improve decision making in newly diagnosed men considering active surveillance and in treated men considering adjuvant therapy or treatment for recurrence. Uncertainty about the risk of disease progression can be reduced if such molecular assays can provide accurate and reproducible prognostic or predictive information beyond NCCN risk group assignment and currently available life expectancy tables and nomograms. Retrospective case cohort studies have shown that these assays provide prognostic information independent of NCCN risk groups, which include likelihood of death with conservative management, likelihood of biochemical recurrence after radical prostatectomy or EBRT, and likelihood of developing metastasis after operation or salvage EBRT. No randomized controlled trials have studied the utility of these tests. Several of these assays are available, and 4 have received positive reviews by the Molecular Diagnostic Program and are likely to be covered by the Centers for Medicare & Medicaid Services. Several other tests are under development, and the use of these assays is likely to increase in the coming year. Although full assessment of their 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. In addition, Decipher may be considered during work up for radical prostatectomy PSA persistence or recurrence (category 2B). Future comparative effectiveness research may allow these tests and others like them to gain additional evidence regarding their utility for better risk stratification of men with prostate cancer.

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) states use of ancillary tests beyond 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.

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 **(E/I)**	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)
81551 **(E/I)**	Oncology (prostate), promoter methylation profiling by real-time RT-PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as likelihood of prostate cancer detection on repeat biopsy
0047U **(E/I)**	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

Copyright © 2019 American Medical Association, Chicago, IL

HCPCS Codes

Code	Description
None	

ICD10 Codes

Code	Description
C61	Malignant neoplasm of prostate
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.

Bishoff JT, et al. Prognostic utility of the cell cycle progression score generated from biopsy in men treated with prostatectomy. J Urol 2014 Aug;192(2):409-14.

BlueCross BlueShield Association. Gene expression analysis for prostate cancer management. Medical Policy Reference Manual Policy #2.04.111. 2017 Nov 09.

Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Microarray-based gene expression analysis for prostate cancer management. TEC Assessments 2013;Volume 28, Tab 11.

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.

Chen H, et al. Adding genetic risk score to family history identified twice as many high-risk men for prostate cancer: results from the Prostate Cancer Prevention Trial. Prostate 2016 Sep;76(12):1120-9.

Chen RC, et al. Active Surveillance for the Management of Localized Prostate Cancer (Cancer Care Ontario Guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement. J Clin Oncol 2016 Jun 20;34(18):2182-90.

Cooperberg MR, et al. Validation of a cell-cycle progression gene panel to improve risk stratification in a contemporary prostatectomy cohort. J Clin Oncol 2013 Apr 10;31(11):1428-4.

Crawford ED, et al. Cell cycle progression score and treatment decisions in prostate cancer: results from an ongoing registry. Curr Med Res Opin 2014;30(6):1025-31.

Cucchiara V, et al. Genomic markers in prostate cancer decision making. Eur Urol 2017 Nov 9 [Epub ahead of print].

Cullen J, et al. A biopsy-based 17-gene genomic prostate score predicts recurrence after radical prostatectomy and adverse surgical pathology in a racial diverse population of men with clinically low- and intermediate-risk prostate cancer. Eur Urol 2015 Jul;68(1):123-31.

Cusick J, 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 2011 Mar;12(3):245-55.

Cusick J, 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. 2015 Jul 28;113(3):382-9.

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.

Falzarano SM, et al. Novel biomarkers and genomic tests in prostate cancer: a critical analysis. Minerva Urol Nefrol. 2015 Sep;67(3):211-31.

Freeland SJ, et al. Prognostic utility of cell cycle progression score in men with prostate cancer after primary external beam radiation therapy. Int J Radiat Oncol Biol Phys 2013 Aug 1;86(5):848-53.

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. 2017 Mar 7[Epub ahead of print].

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.

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.

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.4.2018. [https://www.nccn.org/professionals/physician_gls/pdf/prostate_blocks.pdf] accessed 11/12/18.

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.

Shore N, et al. Clinical utility of a biopsy-based cell cycle gene expression assay in localized prostate cancer. Curr Med Res Opin 2014;30(4):547-53.

*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 no National Coverage Determination (NCD) or Local Coverage Determination (LCD) for gene expression analysis for prostate cancer management. However, effective 10/01/15 the Medicare Part-B carrier for California, Noridian Healthcare Solutions, established a favorable local Coverage Decision for the Molecular Diagnostic Tests for the Confirm MDx® Prostate Cancer Assay. This covers most of Medicare beneficiaries in all 50 states since the MDxHealth reference laboratory in Irvine, California, is within the sole jurisdiction of NHIC for purposes of Part-B coverage. Please refer to: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=36327&ver=16&CntrctrSelected=363*1&Cntrctr=363&s=6&DocType=Active&bc=AggAAAQBAAAA&

There is currently no National Coverage Determination (NCD) or Local Coverage Determination (LCD) for gene expression analysis for prostate cancer management. However, effective 10/15/15 the Medicare Part-B carrier for Utah, Noridian HealthCare Solutions, established a favorable local Coverage Decision for the Molecular Diagnostic Tests for the Prolaris® Prostate Cancer Genomic Assay. This covers most of Medicare beneficiaries in all 50 states since the Myriad reference laboratory in Salt Lake City, UT, is within the sole jurisdiction of NHIC for purposes of Part-B coverage. Please refer to https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=36350&ver=21&CntrctrSelected=348*1&Cntrctr=348&s=52&DocType=Active&bc=AggAAAIBAAAA&

There is currently no National Coverage Determination (NCD) or Local Coverage Determination (LCD) for gene expression analysis for prostate cancer management. However, effective 07/05/16 the Medicare Part-B carrier for California, Noridian Healthcare Solutions, established a favorable local Coverage Decision for the Molecular Diagnostic Tests for the OncotypeDx® Prostate Cancer Assay. This covers most of Medicare beneficiaries in all 50 states since the MDxHealth reference laboratory in Irvine, California, is within the sole jurisdiction of NHIC for purposes of Part-B coverage. Please refer to: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=36364&ver=8&CntrctrSelected=360*1&Cntrctr=360&s=6&DocType=Active&bc=AggAAAIBAAAA&

There is currently no National Coverage Determination (NCD) or `Local Coverage Determination (LCD) for gene expression analysis for prostate cancer management. However, effective 07/05/16 the Medicare Part-B carrier for California, Noridian Healthcare Solutions, established a favorable local Coverage Decision for the Molecular Diagnostic

Tests for the Decipher® Prostate Cancer Classifier Assay. This covers most of Medicare beneficiaries in all 50 states since the MDxHealth reference laboratory in Irvine, California, is within the sole jurisdiction of NHIC for purposes of Part-B coverage. Please refer to: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=36343&ver=22&CntrctrSelected=363*1&Cntrctr=363&s=6&DocType=Active&bc=AggAAAQBAAAA&