Policy Name: Genetic Testing for Prostate Cancer
Effective Date: 5/19/2021

Important Information – Please Read Before Using This Policy

These services may or may not be covered by all Medica plans. Please refer to the member’s plan document for specific coverage information. If there is a difference between this general information and the member’s plan document, the member’s plan document will be used to determine coverage. With respect to Medicare and Minnesota Health Care Programs, this policy will apply unless those programs require different coverage. Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions about this Medica coverage policy may call the Medica Provider Service Center toll-free at 1-800-458-5512.

Medica coverage policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care and treatment.

Coverage Policy

Decipher® Prostate Cancer Classifier Assay, OncotypeDx® Genomic Prostate Score, Prolaris®, and ProMark® Proteomic Prognostic Test, are COVERED when performed on prostate biopsy or radical prostatectomy (RP) specimens, and the patient’s risk stage as defined by the current National Comprehensive Cancer Network (NCCN) guidelines, is one of the following:
1. Men with low- or favorable intermediate-risk disease and life expectancy equal or greater than 10: Patient is considering conservative therapy and the test results of the prostate biopsy will be used when making a decision about active surveillance, or
2. Men with unfavorable intermediate- (adverse laboratory-PSA/pathologic features-Gleason score) or high-risk disease, and life expectancy equal or greater than 10: Test results will be used when making a decision about postoperative secondary therapy (e.g., radiation therapy, adjuvant or early salvage therapy) following radical prostatectomy.

All other uses of Decipher® Prostate Cancer Classifier Assay, OncotypeDx® Genomic Prostate Score, Prolaris®, and ProMark® Proteomic Prognostic Test are considered investigative and unproven and therefore NOT COVERED. There is insufficient reliable evidence in the form of high quality peer-reviewed medical literature to establish the safety and efficacy or effects on health care outcomes.

All other gene expression profiling and biomarkers tests for prostate cancer not listed above are considered investigative and unproven and therefore NOT COVERED. There is insufficient reliable evidence in the form of high quality peer-reviewed medical literature to establish the safety and efficacy or effects on health care outcomes. Examples of these tests include but are not limited to:
1. Prostate Cancer Antigen 3 (PCA3) Analysis
2. deCODE ProstateCancer™
3. Proveri Prostate Cancer Assay (PPCA™)
4. Systems Pathology Testing
5. ConfirmMDx® for Prostate Cancer
6. SelectMDx for Prostate Cancer
Medica Coverage Policy

Note: See also related Medica coverage policies: Liquid Biopsy: Testing of Circulating Tumor Cells or Cell-Free Tumor DNA, Gene Expression Profiling for Assessing Cancers of Unknown Origin, and Genetic and Pharmacogenetic Testing.

Description

Prostate cancer is a complex, heterogeneous disease. Although localized prostate cancers may appear very similar clinically at diagnosis, they often exhibit diverse risk of progression that may not be captured by clinical risk categories or prognostic tools based on clinical findings, including PSA titers, Gleason grade, or tumor stage. Some prostate cancers will manifest as aggressive tumors that metastasize readily and may cause mortality. In other cases, the tumor remains indolent and does not progress to cause extreme morbidity.

Gene expression profile and biomarkers analysis have been proposed as a means to risk-stratify patients with prostate cancer to guide treatment decisions. In vitro gene expression prognostic assays measure gene expression in tumor tissue samples or from prostate biopsy samples to provide a personalized risk score indicative of a tumor’s aggressiveness and may also provide a long-range prostate cancer-specific mortality risk score.

The National Comprehensive Cancer Network® (NCCN) guidelines for prostate cancer (V2.2021) encourages physicians to consider molecular testing of a patient’s tumor post-biopsy when prostate cancer presents as low- or favorable intermediate-risk and life expectancy is greater than or equal to 10 years.

NCCN risk group stages are defined by one of the following:

- Very Low Risk Disease (T1c AND Gleason Score ≤ 6 AND PSA ≤ 10 ng/mL AND <3 prostate cores with tumor AND ≤ 50% cancer in any core AND PSA density of < 0.15 ng/mL/g).
- Low Risk Disease (T1-T2a AND Gleason Score ≤ 6 AND PSA ≤ 10 ng/mL).
- Intermediate: Has no high or very high risk features and has one or more intermediate risk factors (IRF): T2b-T2c or Gleason score 3+4/Gleason grade group 2 or Gleason score 4+3=7/Gleason grade group 3 or PSA level 10-20 ng/mL:
  - Favorable intermediate: 1 IRF and Grade Group 1 or 2 and < 50% biopsy cores positive
  - Unfavorable intermediate: 2 or 3 IRFs and/or Grade Group 3 and/or ≥ 50% biopsy cores positive.
- High: T3a or Gleason score 8/Gleason grade 4 or Gleason score 9-10/Gleason grade 5 or PSA level > 20 ng/mL.
- Very High: T3b-T4 OR Primary Gleason Pattern 5 OR >4 cores with Grade Group 4 or 5.

Risk stratification is combined with patient age, life expectancy, and treatment preferences to make initial therapy decisions.

Examples of genes in multiple test panels include, but are not limited to:

1. Oncogenes: c-myc, mkp-1, bcl-2, RASSF1A, DAB2IP, HER2, EGFR (also known as HER1 or c-erbB-1), HOXB13, TMPRSS2, ETS transcription family members (ERG, ETV1, ETV4, and ETV5), and MMAC1.
2. Tumor suppressor genes: PTEN, MMC1, Mxi1, GSTP1, p53, TGF-b1, CDK11B, NKx3.1, KLF6, and KAI-1. A variety of different genetic biomarker tests are offered to aid in risk assessment, diagnosis, management, and prognosis of prostate cancer. To date these include:
   1. Prostate cancer antigen 3 (PCA3) Testing. The PCA3 gene, found on chromosome 9, is overexpressed in prostate cancer resulting in non-coding, messenger RNA (mRNA) being detected in urine samples obtained immediately following digital rectal exam. The test is purported for use in guiding treatment for individuals with elevated prostate specific antigen (PSA) levels, but negative initial biopsy results, who are considering a follow-up biopsy.
   2. Single-nucleotide polymorphism (SNP) testing. SNPs are single-nucleotide polymorphisms (i.e., one letter variations in one of the bases of the nucleotide pair). Although the genes and biological mechanisms for these SNP associates are not yet confirmed, several SNPs have been identified that appear to be related to prostate cancer risk. Currently, the use of algorithms incorporating results from testing multiple SNPs are being developed in order to increase validity of testing. One test commercially available is deCODE ProstateCancer™, a proprietary methodology identifying genetic variants purported to be markers of risk for prostate cancer in the general population.
3. **Multi-gene expression profiles.** Expression profiles using quantitative measurement of gene expression related to cell cycle progression are suggested for use in predicting the likelihood of tumor recurrence. Three tests are currently available. Prolaris® (Myriad) is a 46-gene profile intended to predict risk for cancer progression. Oncotype DX Prostate Cancer Assay (Genomic Health) is a 17-gene assay using an algorithm to report an individual’s genomic prostate score (GPS). The Decipher® Prostate Cancer Classifier (GenomeDx) is a 22-biomarker test intended to predict the likelihood of developing metastasis within five years of radical prostatectomy or within three years of biochemical recurrence.

4. **Stromal cell gene expression.** The Proveri Prostate Cancer Assay (PPCA™), a proprietary microarray test developed to measure changes in gene expression within stromal cells adjacent to a prostate tumor is intended to be used to clarify results in suspicious negative or equivocal tissue biopsies. Currently, the Proveri Prostate Cancer Assay (Proveri Inc.) has been taken off the market and is no longer available.

5. **Candidate gene diagnosis panels/genome-wide association tests.** No single gene marker has been found that displays both high sensitivity and high specificity for diagnosing prostate cancer. While each gene variant only slightly alters risk, it is theorized that combinations of these gene variants (candidate genes) in an individual places him at higher overall risk for prostate cancer. Therefore, laboratory tests combining several gene markers into single diagnostic panels for prostate cancer are currently under development.

6. **Epigenomic biomarkers (gene hypermethylation).** Assays are being studied that would identify epigenetic changes (i.e., protein modifications at the chromatin level that do not change underlying DNA sequencing, but nonetheless result in changes in gene expression) that appear linked to risk of prostate cancer.

7. **Transmembrane protease, serine (TMPRSS) fusion gene analysis.** TMPRSS2 production is androgen-regulated and is expressed in normal prostate tissue. In prostate cancer, TMPRSS can become fused to the ETS transcription factor family of modulators, which can then affect cell growth, transformation, and apoptosis (i.e., programmed cell death). Fusion genes can be detected in both tissue and urine. It has been suggested that fusion genes are associated with a greater chance of aggressive disease and/or disease recurrence.

8. **Systems Pathology Testing.** Systems pathology is an approach to risk prediction, which involves integrating clinical and pathological variables with tissue imaging and biomarker data. Aureon Biosciences developed two tests using this model, Prostate Px®+ and Post-Op Px®. Prostate Px®+ uses initial biopsy tissue to aid in diagnosis of disease progression for patients considering surgery or other treatment options. Post-Op Px® is done post-surgically using a small amount of tissue removed during a prostatectomy to estimate the postsurgical risk of recurrence and disease. Aureon Laboratories appears to have ceased operations and the Prostate Px and the Post-Op Px tests are no longer available.

9. **Proteomic Prognostic Test.** Automated quantitative imaging method to measure protein biomarkers by immunofluorescent staining in defined areas in intact formalin-fixed paraffin-embedded biopsy tissue, in order to provide independent prognostic information to aid in the stratification of patients with prostate cancer to active surveillance or therapy.

FDA Approval
Genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. Premarket approval from the FDA is not required as long as the assay is performed in a laboratory facility that observes CLIA regulations and the test is not marketed for general distribution. Examples of proprietary genetic tests for prostate cancer include, but are not limited to: (1) ConfirmMDx (MDxHealth), (2) Decipher® Prostate Cancer Classifier, (3) deCODE ProstateCancer, (4) Oncotype DX® Prostate, (5) ProMark® Proteomic, and (6) Prolaris® (Myriad).

In 2012, the FDA approved the PROGENSA® PCA3 as an aid in determination of the need for repeat prostate biopsies in men who have had a previous negative biopsy. Other available PCA3 tests include the PCA3 ProfileR™ and the PCA3 Detection Test. PCA3 genetic testing is being offered by multiple reference laboratories within the United States including, but not limited to, ARUP Laboratories, Bostwick Laboratories, Laboratory Corporation of America (LabCorp), Mayo Medical Laboratories, Quest Diagnostics, and University of Michigan Department of Pathology.

Two tests no longer available are: (1) Proveri Prostate Cancer Assay (Proveri Inc.), and (2) Systems Pathology Testing (Aureon Laboratories).
Prior Authorization
Prior authorization is not applicable. Claims for this service are subject to retrospective review and denial of coverage, as investigative services are not eligible for reimbursement.

Coding Considerations
Use the current applicable CPT/HCPCS code(s). The following codes are included below for informational purposes only, and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

CPT Codes:
- 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
- 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
- 0011M - Oncology, prostate cancer, mRNA expression assay of 12 genes (10 content and 2 housekeeping), RT-PCR test utilizing blood plasma and/or urine, algorithms to predict high-grade prostate cancer risk
- 0005U - Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score
- 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
- 0053U - Oncology (prostate cancer), FISH analysis of 4 genes (ASAP1, HDAC9, CHD1 and PTEN), needle biopsy specimen, algorithm reported as probability of higher tumor grade
- 0113U - MiPS (Mi-Prostate Score) [MLabs, MLabs]
- 0133U - +RNAinsight™ for ProstateNext®, Ambry Genetics
- 0228U - Oncology (prostate), multianalyte molecular profile by photometric detection of macromolecules adsorbed on nanosponge array slides with machine learning, utilizing first morning voided urine, algorithm reported as likelihood of prostate cancer
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Re-Review Date(s):
10/23/2012
11/18/2015
  1/1/2018 – administrative update; codes added
  5/16/2018
11/1/2019 – administrative update; codes added
2/10/2020 – administrative update; format
1/1/2021 – administrative update; code update

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