


<b>MEDICAL POLICY</b>	<b>Prostate: Protein Biomarkers and Genetic Testing (Medicare Only)</b>
<b>Effective Date: 4/1/2021</b>	Medical Policy Number: 95
 4/1/2021	Medical Policy Committee Approved Date: 10/16; 12/17; 1/18; 3/18; 8/18; 8/19; 9/19; 11/19; 2/2020; 3/2021
Medical Officer	Date

**See Policy CPT CODE section below for any prior authorization requirements**

**SCOPE:**

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

**APPLIES TO:**

Medicare Only

<b>MEDICARE POLICY CRITERIA</b>	
<p>The following Centers for Medicare &amp; Medicaid Services (CMS) guidelines should be utilized for medical necessity coverage determinations. Click the link provided in the table below to access applicable medical necessity criteria. All listed guidelines apply.</p>	
Service	Medicare Guidelines
<i>4Kscore Assay</i>	<ul style="list-style-type: none"> <li>• Local Coverage Determination (LCD): MoIDX: 4Kscore Assay (<a href="#">L37122</a>)<sup>1</sup></li> <li>• Local Coverage Article: Billing and Coding: MoIDX: 4Kscore Assay (<a href="#">A57337</a>)<sup>2</sup></li> </ul>
<i>Decipher® Prostate Cancer Classifier Assay</i>	<ul style="list-style-type: none"> <li>• Local Coverage Determination (LCD): MoIDX: Prostate Cancer Genomic Classifier Assay for Men with Localized Disease (<a href="#">L38341</a>)<sup>3</sup></li> <li>• Local Coverage Article: Billing and Coding: MoIDX: Prostate Cancer Genomic Classifier Assay for Men with Localized Disease (<a href="#">A57236</a>)<sup>4</sup></li> </ul> <p><i>For dates of service from 03/01/2020 to 12/05/2020:</i></p> <ul style="list-style-type: none"> <li>○ Local Coverage Determination (LCD): MoIDX: Decipher® Prostate Cancer Classifier Assay (<a href="#">L36345</a>)<sup>5</sup></li> </ul>

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	<ul style="list-style-type: none"> <li>▪ <i>When used to determine which patients traditionally considered high risk of recurrence after radical prostatectomy may be closely followed rather than receive post-operative radiation therapy.</i> <ul style="list-style-type: none"> <li>○ Local Coverage Determination (LCD): MoIDX: Decipher® Prostate Cancer Classifier Assay for Men with Very Low and Low Risk Disease (<a href="#">L37820</a>)<sup>6</sup></li> </ul> </li> </ul> <p><i>For men with intermediate risk disease and dates of service from 03/01/2020 to 11/07/2020:</i></p> <ul style="list-style-type: none"> <li>○ Local Coverage Determination (LCD): MoIDX: Decipher® Prostate Cancer Classifier Assay for Men with Intermediate Risk Disease (<a href="#">L38166</a>)<sup>7</sup></li> </ul>
<i>ConfirmMDx Epigenetic Molecular Assay</i>	<ul style="list-style-type: none"> <li>• Local Coverage Determination (LCD): MoIDX: ConfirmMDX® Epigenetic Molecular Assay (<a href="#">L36329</a>)<sup>8</sup></li> <li>• Local Coverage Article: Billing and Coding: MoIDX: ConfirmMDx Epigenetic Molecular Assay (<a href="#">A57606</a>)<sup>9</sup></li> </ul>
<i>Oncotype DX® Genomic Prostate Score Assay</i>	<ul style="list-style-type: none"> <li>• Local Coverage Determination (LCD): MoIDX: Genomic Health™ Oncotype DX® Prostate Cancer Assay (<a href="#">L36368</a>)<sup>10</sup></li> <li>• Local Coverage Article: Billing and Coding: MoIDX: Oncotype DX® Genomic Prostate Score (<a href="#">A56372</a>)<sup>11</sup></li> <li>• Local Coverage Determination (LCD): MoIDX: ONCOTYPE DX® Genomic Prostate Score for Men with Favorable Intermediate Risk Prostate Cancer (<a href="#">L37321</a>)<sup>12</sup></li> <li>• Local Coverage Determination (LCD): MoIDX: Prostate Cancer Genomic Classifier Assay for Men with Localized Disease (<a href="#">L38341</a>)<sup>3</sup></li> <li>• Local Coverage Article: Billing and Coding: MoIDX: Prostate Cancer Genomic Classifier Assay for Men with Localized Disease (<a href="#">A57236</a>)<sup>4</sup></li> </ul>
<i>Oncotype DX® AR-V7 Nucleus Detect Test</i>	<ul style="list-style-type: none"> <li>• MoIDX: Androgen Receptor Variant (AR-V7) Protein Test (<a href="#">L37744</a>)<sup>13</sup></li> <li>• Local Coverage Article: Billing and Coding: MoIDX: Androgen Receptor Variant (AR-V7) Protein Test (<a href="#">A57291</a>)<sup>14</sup></li> </ul>
<i>ProgenSA® PCA3 Assay</i>	<ul style="list-style-type: none"> <li>• Local Coverage Determination (LCD): MoIDX: Molecular Diagnostic Tests (MDT) (<a href="#">L36256</a>)<sup>15</sup></li> <li>• Local Coverage Article: Billing and Coding: MoIDX: ProgenSA® PCA3 Assay (<a href="#">A54492</a>)<sup>16</sup></li> </ul>
<i>Prolaris® Prostate Cancer Genomic Assay</i>	<ul style="list-style-type: none"> <li>• Local Coverage Determination (LCD): MoIDX: Prolaris™ Prostate Cancer Genomic Assay (<a href="#">L36350</a>)<sup>17</sup></li> <li>• Local Coverage Article: Billing and Coding: MoIDX: Prolaris™ Prostate Cancer Genomic Assay (<a href="#">A57511</a>)<sup>18</sup></li> <li>• Local Coverage Determination (LCD): MoIDX: Prolaris™ Prostate Cancer Genomic Assay for Men with Favorable Intermediate Risk Disease (<a href="#">L37082</a>)<sup>19</sup></li> </ul>

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	<ul style="list-style-type: none"> <li>Local Coverage Article: Billing and Coding: MoIDX: Prolaris™ Prostate Cancer Genomic Assay for Men with Favorable Intermediate Risk Disease (<a href="#">A57691</a>)<sup>20</sup></li> </ul>
<i>ProMark Risk Score</i>	<ul style="list-style-type: none"> <li>Local Coverage Determination (LCD): MoIDX: ProMark Risk Score (<a href="#">L36706</a>)<sup>21</sup></li> <li>Local Coverage Article: Billing and Coding: MoIDX: ProMark Risk Score (<a href="#">A57609</a>)<sup>22</sup></li> </ul>

*Per the [Medicare Policy Manual](#) commercial medical policies may be applied to Medicare coverage determinations in the absence of an appropriate NCD, LCD, LCA, or CMS Coverage Manual. Therefore, the commercial medical policy, **Prostate: Protein Biomarkers and Genetic Testing (All Lines of Business Except Medicare)**, may apply to any services not addressed by Medicare above.*

## POLICY GUIDELINES

### PCA3 Guidelines

Effective 10/15/2012, MoIDX will deny all laboratory developed tests (LDT) for PCA3 as statutorily excluded services that do not support the required clinical utility for the established Medicare benefit category. Only the unmodified FDA approved test, will be reimbursed.

## BILLING GUIDELINES

For applicable billing guidelines, please see:

- Local Coverage Article: Billing and Coding: MoIDX: Prostate Cancer Genomic Classifier Assay for Men with Localized Disease ([A57236](#))<sup>4</sup>
- Local Coverage Article: MoIDX: Oncotype DX Genomic Prostate Score Coding and Billing Article ([A56372](#))<sup>11</sup>
- Local Coverage Article: Progensa® PCA3 Assay Billing and Coding guidelines ([A54492](#))<sup>23</sup>

According to the LCDs and LCAs listed above, CMS has indicated that a number of the assays addressed in the policy be billed with specific codes.

Assay	Code	Note
4K score	81539	
ConfirmMDx	81479, 81551	81551 is a new code effective 1/1/18.
Decipher	81479	

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Oncotype	81479, 0047U	0047U is a new code effective 7/1/2018
PCA3	81313	
Prolaris	81479, 81541	81541 is a new code effective 1/1/18.
ProMark	81479	

## CPT CODES

Medicare Only	
Prior Authorization Required	
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
81313	PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)
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
81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis 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
Not Covered	
0005U	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score
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
0021U	Oncology (prostate), detection of 8 autoantibodies (ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2),
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	Oncology (prostate), measurement of PCA3 and TMPRSS2-ERG in urine and PSA in serum following prostatic massage, by RNA amplification and fluorescence-based detection, algorithm reported as risk score
0133U	Hereditary prostate cancer–related disorders, targeted mRNA sequence analysis panel (11 genes) (List separately in addition to code for primary procedure)

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81539	Oncology (high-grade prostate cancer), biochemical assay of four proteins (Total PSA, Free PSA, Intact PSA, and human kallikrein-2 [hK2]), utilizing plasma or serum, prognostic algorithm reported as a probability score
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<p><b>Unlisted Codes</b>  All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then <b>prior-authorization is required.</b></p>	
81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis
84999	Unlisted chemistry code

**DESCRIPTION**

Test Descriptions

*4Kscore Test*

The 4Kscore test consists of a panel of four kallikreins in blood that is supposed to reduce unnecessary biopsy in men being considered for biopsy of the prostate for potential cancer. The clinical features of this group are poorly defined. The kallikreins consist of total PSA, free PSA, intact PSA and kallikrein-related peptidase 2 (hK2).

*Confirm MDx*

Confirm MDx assesses the methylation status of 3 biomarkers (GSTP1, RASSF1, APC) associated with PROSTATE cancer. Confirm MDx 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 (HGPI)) in the previous biopsy, and is being considered for repeat biopsy. Several case/control studies in archived biopsy core tissue blocks demonstrated the sensitivity, specificity and high negative predictive value (NPV) of these biomarkers to predict cancer detection in a repeat biopsy procedure. Single biopsy cores, using as little as 20 microns from formalin-fixed, paraffin embedded (FFPE) tissue blocks or sections cut from blocks fixed on glass slides are used in this assay.

*Decipher® Prostate Cancer Classifier Assay*

The Decipher® prostate cancer assay, a 22-biomarker expression signature using oligonucleotide microarray technology, interrogates 1.4 million RNAs extracted from a formalin-fixed paraffin embedded (FFPE) tissue block of the index lesion (defined by highest tumor stage or histological Gleason grade) from the RP specimen. The biomarkers that comprise the Decipher classifier include cell cycle

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progression, androgen signaling, cell adhesion, tumor cell motility, migration and immune evasion functions.

*Oncotype DX® Prostate Cancer Assay Prostate Cancer Assay*

Oncotype DX® Prostate Cancer Assay is prostate biopsy-based 17-gene RT-PCR assay, representing four molecular pathways (androgen signaling, cellular organization, stromal response and proliferation), that provides a biologic measure of cancer aggressiveness. The assay is indicated for men who are considered candidates for active surveillance (AS) (those with NCCN® very low- and low-risk prostate cancer). The assay is designed to inform decisions between AS and immediate treatment.

*Progenesa® PCA3 Assay*

Progenesa® PCA3 Assay, an FDA approved test by Gen-Probe Incorporated, is an mRNA expression assay used alone or in combination with other molecular tests for PROSTATE cancer determination to identify patients with increased risk of PROSTATE cancer. PCA3 may help to improve the specificity of PROSTATE cancer detection providing additional information about the risk of PROSTATE cancer over the use of the PSA test alone. Based on the ratio of PCA3 mRNA/PSA mRNA x1000, the PCA3 assay is performed on the first urine collected following an attentive digital rectal examination.

*Prolaris™ Prostate Cancer Assay*

Prolaris™ is an RNA based assay measuring the expression of 31 cell cycle progression (CCP) genes and 15 “housekeeping” genes that act as internal controls and normalization standards in each patient sample. The assay is performed on formalin fixed paraffin-embedded (FFPE) prostate cancer blocks. The assay results are reported as a numerical score along with accompanying interpretive information.

*ProMark Test*

ProMark is a biopsy-based prostate cancer prognostic test that utilizes an automated, quantitative protein-based multiplex immunofluorescent in situ imaging platform to evaluate standard formalin-fixed, paraffin-embedded prostate tissue to differentiate indolent from aggressive prostate cancer). The assay measures the signal intensity of 8 protein biomarkers (i.e., CUL2, DERL1, FUS, HSPA9, PDSS2, pS6, SMAD4 and YBX1) in tumor and benign prostate glands on FFPE biopsy tissue sections to generate an algorithmically derived risk score indicating the likelihood of having high-risk disease. Unlike DNA/RNA-based tests that require biopsy tissue to be homogenized prior to analysis, PROMARK technology allows for analysis of proteins directly from the cancerous regions of interest. The test has shown the ability to predict prostate cancer aggressiveness regardless from which region the prostate biopsy was taken, a key feature and benefit given the considerable heterogeneity that exists in biopsied tissue.

**INSTRUCTIONS FOR USE**

## MEDICAL POLICY

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Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days' notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

## REGULATORY STATUS

### Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

## REFERENCES

1. Centers for Medicare & Medicaid Services. Local Coverage Determination (LCD): MoIDX: 4Kscore Assay (L37122). Effective 11/01/2019. <https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=37122>. Accessed 1/31/2021.
2. Centers for Medicare & Medicaid Services. Local Coverage Article: Billing and Coding: MoIDX: 4Kscore Assay (A57337). Effective 11/1/2019. <https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=57337>. Accessed 1/30/2021.
3. Centers for Medicare & Medicaid Services. Local Coverage Determination (LCD): MoIDX: Prostate Cancer Genomic Classifier Assay for Men with Localized Disease (L38341). Effective 12/06/2020. <https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?lcdid=38341>. Accessed 4/22/2021.
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5. Centers for Medicare & Medicaid Services. Local Coverage Determination (LCD): MoIDX: Decipher® Prostate Cancer Classifier Assay (L36345). Retired 12/05/2020. <https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=36345>. Accessed 01/02/2021.

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8. Centers for Medicare & Medicaid Services. Local Coverage Determination (LCD): MoIDX: ConfirmMDX® Epigenetic Molecular Assay (L36329). Effective 12/10/2020. <https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=36329>. Accessed 1/31/2021.
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