

Molecular Biomarkers for Prostate Cancer Risk Stratification



INDEPENDENT CARE HEALTH PLAN

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Medicare Advantage Medical Coverage Policy

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Disclaimer

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Related Medicare Advantage Medical/Pharmacy Coverage Policies

Gene Expression Profiling for Cancer Indications

Genetic Testing

Genetic Testing for Hereditary Breast, Ovarian, Pancreatic and Prostate Cancer

Multianalyte Assays with Algorithmic Analyses for Cancer Indications

Related Documents

Please refer to [CMS website](#) for the most current applicable National Coverage Determination (NCD)/Local Coverage Determination (LCD)/Local Coverage Article (LCA)/CMS Online Manual System/Transmittals.

Molecular Biomarkers for Prostate Cancer Risk Stratification

Type	Title	ID Number	Jurisdiction Medicare Administrative Contractors (MACs)	Applicable States/Territories
LCD	MolDX: Molecular Biomarkers to Risk-Stratify Patients at Increased Risk for Prostate Cancer	L39042	J5, J8 - Wisconsin Physicians Service Insurance Corporation	IA, IN, KS, MI, MO, NE
	ProMark® Risk Score	L37011		
LCD	Biomarker Testing for Prostate Cancer Diagnosis	L37733	J6, JK- National Government Services, Inc.	CT, IL, ME, MA, MN, NH, NY, RI, VT, WI
LCD	MolDX: Molecular Biomarkers to Risk-Stratify Patients at Increased Risk for Prostate Cancer	L38997	J15 - CGS Administrators, LLC	KY, OH
	ProMark® Risk Score	L36675		
	Prostate Cancer Detection with IsoPSA®	L39284		
LCD	MolDX: Molecular Biomarkers to Risk-Stratify Patients at Increased Risk for Prostate Cancer	L39005	JE - Noridian Healthcare Solutions, LLC	CA, HI, NV, American Samoa, Guam, Northern Mariana Islands
	ProMark® Risk Score	L36704		
LCD	MolDX: Molecular Biomarkers to Risk-Stratify Patients at Increased Risk for Prostate Cancer	L39007	JF - Noridian Healthcare Solutions, LLC	AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY
	ProMark® Risk Score	L36706		
LCD	4Kscore Test Algorithm	L37792	JH, JL - Novitas Solutions, Inc.	AR, CO, DE, LA, MD, MS, NJ, NM, OK, PA, TX, D.C.
	Biomarkers for Oncology	L35396		
LCD	4Kscore® Assay	L36763	JJ, JM - Palmetto GBA	AL, GA, NC, SC, TN, VA, WV
	MolDX: Molecular Biomarkers to Risk-Stratify Patients at	L38985		

	Increased Risk for Prostate Cancer ProMark® Risk Score	L36665		
LCD	4Kscore Test Algorithm	L37798	JN - First Coast Service Options, Inc.	FL, PR, U.S. VI

Description

While prostate specific antigen (PSA) testing is considered the gold standard for prostate cancer screening and management, molecular markers may improve sensitivity and specificity. Prostate biomarkers have been developed to risk stratify an individual at risk of high-grade prostate cancer. These tests are also used for those with low grade or slow growing cancer, allowing for the potential avoidance of unnecessary biopsies and interventions. These biomarkers are typically noninvasive (blood or urine based).

4Kscore measures the blood plasma levels of four proteins (total PSA, free PSA, intact PSA and human kallikrein2 [hK2]) and uses an algorithm to combine the results with age, digital rectal exam (DRE) and prior prostate biopsy results. The result purports to identify an individual's specific probability for finding a high-grade prostate cancer upon biopsy.

Apifyn is a blood test that measures eight autoantibodies released by the immune system in response to the presence of prostate cancer and may aid in the assessment of risk for prostate cancer.

ArteraAI Prostate Test is a multimodal artificial intelligence (MMAI) prognostic biomarker that has been developed to identify an individual with high-risk prostate cancer who may benefit from therapy personalization. The test utilizes a proprietary algorithm that assesses digital images from an individual's prostate biopsy and learns from the individual's clinical data. The AI combines this information to determine if an individual may benefit from hormone therapy as well as estimate prognosis.

IsoPSA is a blood test that measures PSA proteins that originate from cancer cells. The test is used to identify men who would not benefit from prostate biopsy.

MyProstateScore 2.0 (MPS2) (formerly Mi-Prostate Score [MiPS]) is the next-generation of the MyProstateScore test. It is a noninvasive urine assay that analyzes gene transcripts and a proprietary algorithm purportedly to predict cancer in an individual with an elevated PSA results and a negative biopsy.

PanGIA Prostate is a multianalyte molecular profiling urine test that uses a proprietary machine learning algorithm purported to assist with prostate biopsy decisions.

Percent-free PSA (%fPSA) is a diagnostic test that assesses the ratio of unbound (free) PSA to total PSA in the bloodstream. In an individual with prostate cancer, this ratio is typically lower than in those without the condition. When a PSA test falls within the borderline range, analyzing the %fPSA can help determine the need for a prostate biopsy. A lower %fPSA suggests an increased likelihood of prostate cancer and warrants consideration for a prostate biopsy.

Prostate cancer antigen 3 (PCA3) is an in vitro nucleic acid amplification test that measures the concentration of PCA3 and PSA in post-digital rectal exam (DRE) first-catch urine specimens. **ProgenSA PCA3** is an example of a US Food & Drug Administration (FDA)-approved PCA3 test.

ProMark Proteomic Prognostic Test is a protein based prognostic test that analyzes 8 biomarkers (*DERL1, CUL2, SMAD4, PDSS2, HSPA9, FUS, pS6, YBOX1*), quantitative immunofluorescence and digitalized quantitative measurements to evaluate for prostate cancer.

Prostate Health Index (PHI) (also be referred to as proPSA) utilizes a calculation that combines the results of three quantitative blood serum immunoassays (PSA, free PSA and p2PSA) into a single numerical result known as a PHI score. This score has been suggested to determine the probability of finding prostate cancer with a biopsy.

Coverage Determination

iCare follows the CMS requirements that only allows coverage and payment for services that are reasonable and necessary for the diagnosis and treatment of illness or injury or to improve the functioning of a malformed body member except as specifically allowed by Medicare.

Genetic tests must demonstrate clinical utility, analytical and clinical validity and fulfill the CMS “reasonable and necessary” criteria. Analytic validity (test accurately identifies the gene variant), clinical validity (test identifies or predicts the clinically defined disorder) and clinical utility (test measurably improves clinical outcomes) of the genetic test is supported by generally accepted standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, specialty society recommendations, and views of physicians practicing in relevant clinical areas. The test must be ordered by a physician who is treating the beneficiary and the results will be used in the management of a beneficiary’s specific medical problem.

For jurisdictions with no Medicare guidance for a particular test, iCare will utilize the [MolDX program](#) and Technical Assessments for molecular assays as the standard to evaluate clinical utility, analytical and clinical validity in conjunction with adhering to Medicare’s reasonable and necessary requirement.

In interpreting or supplementing the criteria above and in order to determine medical necessity consistently, iCare may consider the following criteria:

General Criteria for Laboratory Analysis for Prostate Cancer

Apply General Criteria for Molecular Biomarkers for Prostate Cancer Risk Stratification when test specific criteria are not available on this medical coverage policy.

Molecular biomarkers for prostate cancer risk stratification may be considered medically reasonable and necessary when the following requirements are met:^{16,17,18,19,20}

- Individual does not have an established diagnosis of prostate cancer; **AND**

- Is a candidate for prostate biopsy or repeat prostate biopsy according to professional society guidelines (eg, National Comprehensive Cancer Network [NCCN], American Society of Clinical Oncology [ASCO], American Urological Association [AUA]); **AND**
- Has not had a prostate biopsy or has a previous negative or nonmalignant but abnormal histopathology finding (ie, atypical small acinar proliferation [ASAP] or high-grade prostatic intraepithelial neoplasia [HGPIN] on prostate biopsy (an individual for repeat biopsy must have first undergone repeat PSA and/or DRE testing as recommended by professional society guidelines [NCCN, ASCO, AUA]); **AND**
- Individual would benefit from treatment of prostate cancer and clinical management will be impacted by use of a biomarker in a manner already demonstrated in the peer-reviewed published literature to improve outcomes; **AND**
- Medical record supports the medical necessity for the biomarker test; **AND**
- Test is performed according to the intended use of the test in the intended patient population for which the test was developed and validated; **AND**
- Test must be performed according to Clinical Laboratory Improvement Amendments (CLIA) and/or US Food and Drug Administration (FDA) regulations in an accredited laboratory; **AND**
- If the test relies on an algorithm which may range in complexity from a threshold determination of a single numeric value to a complex mathematical or computational function, the algorithm must be validated in a cohort that is not a development cohort for the algorithm; **AND**
- Analytic validity, clinical validity and clinical utility of the test is supported by the [MolDX program](#); **AND**
- Test is ordered by a physician specialist in the management of prostate cancer, such as a urologist or oncologist. (An exception may be made in geographic locations where the specialist(s) cannot be reasonably reached by the individual and the ordering provider is located closer to the individual's place of residence than the nearest specialist (generally an individual that lives in a rural location, islands or some other location where access to care is limited); **AND**
- For a given clinical indication (pre- or post-biopsy), only one molecular biomarker may be performed unless a second test is reasonable and necessary as an adjunct to the first test and meets all the above criteria; **AND**
 - Individual to be tested is 75 years of age or younger and prostate specific antigen (PSA) (or adjusted PSA for an individual taking 5-alpha-reductase inhibitors) is greater than 3 ng/mL and less than 10 ng/mL and/or digital rectal exam (DRE) findings are very suspicious of prostate cancer; **OR**
 - Individual to be tested is more than 75 years of age and PSA (or adjusted PSA) is greater than or equal to 4 ng/mL and less than 10 ng/mL and/or DRE findings are very suspicious for prostate cancer; **OR**

- Individual to be tested has a PSA level greater than 10 ng/mL and is a candidate for repeat biopsy according to consensus guidelines (eg, National Comprehensive Cancer Network [NCCN], American Society of Clinical Oncology [ASCO], American Urological Association [AUA]) when the specific biomarker has been validated in an individual with a PSA level greater than 10 ng/mL and multiparametric magnetic resonance imaging (mpMRI) is negative, if performed

Criteria for Specific Tests

4Kscore* (81539) will be considered medically reasonable and necessary when the following requirements are met:^{12,13}

- Individual does not have an established diagnosis of prostate cancer; **AND**
- Evidence of shared decision making between the ordering provider and the beneficiary; **AND**
- All components of the algorithm are present including the following;
 - 4 Kallikreins proteins (total PSA [tPSA], free PSA [fPSA], intact PSA [iPSA] and human kallikrein-2 [hK2]); **AND**
 - Clinical information including age; **AND**
 - DRE; **AND**
 - Prior biopsy history; **AND**
- Individual to be tested is 45 years of age or older; **AND**
- Test is performed prior to initial biopsy or following a negative biopsy; **AND**
- **Confirmed**** moderately elevated prostate PSA (greater than 3 and less than 10 ng/mL; greater than or equal to 4 and less than 10 ng/mL in an individual older than 75 years of age; **AND**
- No other **relative indication***** for prostate biopsy including any of the following (this may not be an all-inclusive list):
 - DRE suspicious for cancer (prostate biopsy should be encouraged); **OR**
 - Persistent and significant increase in PSA (prostate biopsy should be encouraged); **OR**
 - Positive multiparametric magnetic resonance imaging (MRI), if performed; **OR**
 - Other major risk factor for prostate cancer including (this may not be an all-inclusive list):
 - Ethnicity at higher risk for prostate cancer
 - **First-degree relative** with prostate cancer

- High-penetrance prostate cancer risk gene(s) per NCCN guidelines (category 1 or 2A recommendation), if known; **AND**
- No other [relative contraindication](#)*** for prostate biopsy including any of the following:
 - Less than a 10 year life expectancy; **OR**
 - Benign disease not ruled out

[IsoPSA Assay](#)* (0359U) will be considered medically reasonable and necessary when the following requirements are met:²⁶

- Individual does not have an established diagnosis of prostate cancer; **AND**
- 50 years of age or older; **AND**
- [Confirmed](#)** moderately elevated PSA (greater than 4 and less than or equal to 25 ng/mL; **AND**
- No other relative contraindication for prostate biopsy (eg, less than 10 year life expectancy)

[MyProstateScore 2.0 \(MPS2\) \(0403U\) \(formerly Mi-Prostate Score \[MiPS\] \(0113U\)*](#), [Percent-free PSA \(%fPSA\)*](#) or [Prostate Health Index*](#) will be considered medically reasonable and necessary when the following requirements are met:¹⁴

- Individual does not have an established diagnosis of prostate cancer; **AND**
 - Test is performed prior to initial prostate biopsy and individual to be tested is at least 50 years of age with PSA greater than 4 ng/mL; **AND**
 - No other relative indication for prostate biopsy including any of the following:
 - ❖ DRE suspicious for cancer (eg, nodules, induration or asymmetry); **OR**
 - ❖ Positive multiparametric MRI (Prostate Imaging Reporting and Data System [PI-RADS] greater than or equal to 3), if available; **OR**
 - ❖ Positive prior biopsy (cancer Histologic Grade Group greater than or equal to 1, intraductal carcinoma [IDC], atypical intraductal proliferation [AIP]); **AND**
 - No other relative contraindication for prostate biopsy including any of the following:
 - ❖ Less than 10 year life expectancy or is otherwise not a candidate for prostate cancer treatment; **OR**
 - ❖ Invasive treatment for benign prostatic disease or taking medications that influence serum PSA levels within 6 months; **OR**
 - ❖ Active prostatitis on antibiotics; **OR**

- Test is performed prior to repeat biopsy in an individual who is at higher risk despite a negative prior prostate biopsy and has a [confirmed](#)** moderately elevated PSA (greater than 3ng/mL and less than 10 ng/mL for an individual 75 years of age or younger or PSA greater than 4 ng/mL and less than 10 ng/mL for an individual greater than 75 years of age); **AND**
 - No other relative indication for prostate biopsy including any of the following:
 - ❖ DRE suspicious for cancer (eg, nodules, induration or asymmetry); **OR**
 - ❖ Positive multiparametric MRI (Prostate Imaging Reporting and Data System [PI-RADS] greater than or equal to 3), if available; **OR**
 - ❖ Positive prior biopsy (cancer Histologic Grade Group greater than or equal to 1, intraductal carcinoma [IDC], atypical intraductal proliferation [AIP]); **OR**
 - ❖ Other major risk factor for prostate cancer including any of the following:
 - Ethnicity at higher risk for prostate cancer (eg, Ashkenazi Jewish ancestry); **OR**
 - [First-degree relative](#) with prostate cancer; **OR**
 - High-penetrance prostate cancer risk gene(s) per NCCN guidelines (category 1 or 2A recommendation), if known; **AND**
 - No other relative contraindication for prostate biopsy including any of the following:
 - ❖ Less than 10 year life expectancy or is otherwise not a candidate for prostate cancer treatment; **OR**
 - ❖ Invasive treatment for benign prostatic disease or taking medications that influence serum PSA levels within 6 months; **OR**
 - ❖ Active prostatitis on antibiotics

PCA3* (eg, Progenesa PCA3 Assay [81313]) will be considered medically reasonable and necessary to determine the need for repeat prostate biopsy in an individual who had a previous negative prostate biopsy and does not have an established diagnosis of prostate cancer.¹⁴

ProMark Proteomic Prognostic Test will be considered medically reasonable and necessary when the following requirements are met:^{21,22,23,24,25}

- Very-low-risk disease defined as:

- T1c; **AND**
- Gleason score less than or equal to 6; **AND**
- PSA less than or equal to 10 ng/mL; **AND**
- Less than or equal to 50% cancer in any core; **AND**
- PSA density of less than 0.15 ng/mL/g); **OR**

- Low-risk disease defined as:
 - T1-T2a; **AND**
 - Gleason score less than or equal to 6; **AND**
 - PSA \leq 10 ng/mL); **AND**

- Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement); **AND**

- Estimated life expectancy of greater than or equal to 10 years; **AND**

- Individual is a candidate for and is considering conservative therapy but would be eligible for definitive therapy (radical prostatectomy, radiation therapy or brachytherapy); **AND**

- Individual has not received pelvic radiation or androgen deprivation therapy prior to the biopsy; **AND**

- Test is ordered by a physician certified in the Metamark Genetics Certification and Training Registry (CTR); **AND**

- Individual is monitored for disease progression according to active surveillance guidelines as recorded in NCCN guidelines (category 1 or 2A recommendations); **AND**

- Physician must report the development of metastasis or prostate cancer deaths in an individual not treated definitively who were deemed low risk by the assay

*One biomarker test, ordered by a physician or other qualified health care professional is covered once per year.¹⁴

**PSA elevation should be verified after a few weeks under standardized conditions (eg, no ejaculation, manipulations and urinary tract infections, no medications such as 5 α -reductase) performed in the same laboratory or other CLIA approved laboratory before considering a biopsy.^{12,13,14,26}

***The relative indications and contraindications are not absolute. When the 4Kscore test is determined to be medically reasonable and necessary for the beneficiary with one of the relative indications or contraindications for prostate biopsy, the medical record must support the medical necessity for the test and there must be documented evidence of shared decision making between the individual and provider. This supporting documentation must be provided to the laboratory at the time of ordering the test.^{12,13}

The use of the criteria in this Medicare Advantage Medical Coverage Policy provides clinical benefits highly likely to outweigh any clinical harms. Services that do not meet the criteria above are not medically necessary and thus do not provide a clinical benefit. Medically unnecessary services carry risks of adverse outcomes and may interfere with the pursuit of other treatments which have demonstrated efficacy.

Coverage Limitations

[US Government Publishing Office. Electronic code of federal regulations: part 411 – 42 CFR § 411.15 - Particular services excluded from coverage](#)

The following tests may not be considered a benefit (statutory exclusion):⁵¹

- Tests considered screening in the absence of clinical signs and symptoms of disease that are not specifically identified by the law; **OR**
- Tests that confirm a diagnosis or known information; **OR**
- Tests to determine risk for developing a disease or condition; **OR**
- Tests performed to measure the quality of a process; **OR**
- Tests without diagnosis specific indications; **OR**
- Tests identified as investigational by available literature and/or the literature supplied by the developer and are not a part of a clinical trial

These treatments and services fall within the Medicare program's statutory exclusion that prohibits payment for items and services that have not been demonstrated to be reasonable and necessary for the diagnosis and treatment of illness or injury (§1862(a)(1) of the Act). Other services/items fall within the Medicare program's statutory exclusion at 1862(a)(12), which prohibits payment.

The following items will not be considered medically reasonable and necessary:

- Genetic tests that have not demonstrated clinical utility, analytical and clinical validity via the [MoIDX Program](#)

A review of the current medical literature shows that the evidence is insufficient to determine that these services are standard medical treatments. There remains an absence of randomized, blinded clinical studies examining benefit and long-term clinical outcomes establishing the value of these services in clinical management.

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
81313	PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)	
81479	Unlisted molecular pathology procedure	
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	
81599	Unlisted multianalyte assay with algorithmic analysis	
84999	Unlisted chemistry procedure	
86316	Immunoassay for tumor antigen, other antigen, quantitative (eg, CA 50, 72-4, 549), each	
0021U	Oncology (prostate), detection of 8 autoantibodies (ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2), multiplexed immunoassay and flow cytometry serum, algorithm reported as risk score	
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	
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	
0359U	Oncology (prostate cancer), analysis of all prostate-specific antigen (PSA) structural isoforms by phase separation and immunoassay, plasma, algorithm reports risk of cancer	

0376U	Oncology (prostate cancer), image analysis of at least 128 histologic features and clinical factors, prognostic algorithm determining the risk of distant metastases, and prostate cancer- specific mortality, includes predictive algorithm to androgen deprivation- therapy response, if appropriate	
0403U	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	
CPT® Category III Code(s)	Description	Comments
No code(s) identified		
HCPCS Code(s)	Description	Comments
No code(s) identified		

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Appendix

Appendix A

Family Relationships

Relationship	Definition
First-degree	Child, full-sibling, parent
Second-degree	Aunt, uncle, grandchild, grandparent, nephew, niece, half-sibling
Third-degree	First cousin, great aunt, great-uncle, great-grandchild, great-grandparent, half-aunt, half-uncle

Change Summary

- 01/01/2024 New Policy.