# *Medicare Medical Policy*

# Protein Biomarker and Genetic Testing for the Prostate

**MEDICARE MEDICAL POLICY NUMBER:** 95

**Effective Date:** 4/1/2025

**Last Review Date:** 3/2025

**Next Annual Review:** 4/2025



**INSTRUCTIONS FOR USE:** Company Medicare Medical Policies serve as guidance for the administration of plan benefits and do not constitute medical advice nor a guarantee of coverage. Company Medicare Medical Policies are reviewed annually to guide the coverage or non-coverage decision-making process for services or procedures in accordance with member benefit contracts (otherwise known as Evidence of Coverage or EOCs) and Centers of Medicare and Medicaid Services (CMS) policies, manuals, and other CMS rules and regulations. In the absence of a CMS coverage determination or specific regulation for a requested service, item or procedure, Company policy criteria or applicable utilization management vendor criteria may be applied. These are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. 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.

The Company reserves the right to determine the application of Medicare Medical Policies and make revisions to these policies at any time. Any conflict or variance between the EOC and Company Medical Policy will be resolved in favor of the EOC.

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

## *PRODUCT AND BENEFIT APPLICATION*

☒ Medicare Only

## MEDICARE COVERAGE CRITERIA

**IMPORTANT NOTE:** More than one Centers for Medicare and Medicaid Services (CMS) reference may apply to the same health care service, such as when more than one coverage policy is available (e.g., both an NCD and LCD exist). All references listed should be considered for coverage decision-making. The Company uses the most current version of a Medicare reference available at the time of publication; however, these websites are not maintained by the Company, so Medicare references and their corresponding hyperlinks may change at any time. If there is a conflict between the Company Medicare Medical Policy and CMS guidance, the CMS guidance will govern.

| Service | Medicare Guidelines |
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| *4Kscore Assay (CPT 81539; BioReference Laboratory; New Jersey)* | Testing performed in the states of NJ, CO, NM, OK, TX, AK, LA, MS, DE, MD, PA:<br>Local Coverage Determination (LCD): 4Kscore Test Algorithm (L37792) *(Apply this LCD for all 4Kscore testing requests)* |
| *EpiSwitch® Prostate Screening Test (PSE) (0433U) (Oxford BioDynamics, Inc.)* | National Coverage Determination (NCD): Prostate Cancer Screening Tests (210.1)<br><br>**NOTE:** The EpiSwitch® Prostate Screening Test is **not medically necessary** based on the above NCD. Coverage of prostate cancer screening tests is limited to a screening digital rectal exam or a screening prostate specific antigen test. See also the member's EOC for prostate cancer screening benefits and the Medicare Preventive Services interactive chart for Prostate Cancer Screening. |
| *Gene Expression Profile Tests for **Castration Resistant and Metastatic Prostate Cancers***<br><br>***Examples include:***<br>*Decipher® Prostate Cancer Classifier Assay (CPT 81542; Decipher Biosciences; California)* ***(This test may also be used for localized [non-metastatic] disease – for these, see the LCDs in the next row)*** | LCD: MolDX: Gene Expression Profile Tests for Decision-Making in Castration Resistant and Metastatic Prostate Cancers<br>• Testing performed in AK, ID, OR, WA, UT, AZ, MT, ND, SD, and WY: L39688<br>• Testing performed in CA and NV: L39686<br>• Testing performed in AL, GA, TN, SC, VA, WV, NC: L39636<br><br>**NOTES**:<br>• Criteria 1-4 are clinical, pertaining to the individual ***patient***.<br>• Criteria 5-10 are criteria pertaining to the specific ***test***. If a test meets criterion #10, it is presumed that test has met criteria 5-9 as well.<br>• These LCDs are specific to **gene expression profile (GEP) tests** only. They do not apply to next-generation sequencing (NGS) or single biomarker expression analysis |

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| | tests. Other references would need to be used to address those testing methods.<br>• For GEP tests performed in service areas **not** listed above, see other sections of this policy. If they are not included in this policy, additional research will be required.<br>• The Decipher® Prostate Cancer Classifier Assay (CPT 81542; Decipher Biosciences; California) **has met** the technical assessment (TA) requirement (Criterion #10) of this LCD.<br>• While the LCDs above specifically call out the *Decipher* test by name, they also state that "**Genomic expression profile tests that demonstrate equivalent or superior analytical and clinical validity to those covered by this contractor will be considered reasonable and necessary for the same indications."**<br>• Therefore, for GEP tests performed in service areas listed above, but not listed in this policy, additional research will be required to determine if they meet this TA criterion, and if the criteria from the above LCDs may also apply to these tests. |
| *Prostate Cancer Assays for* ***Localized Disease***<br><br>***Examples include:***<br>*Decipher® Prostate Cancer Classifier Assay (CPT 81542; Decipher Biosciences; California)*<br><br>*Genomic Prostate Score® (GPS) Test (CPT 0047U; Genomic Health; California)*<br><br>*Prolaris® Prostate Cancer Genomic Assay (CPT 81541; Myriad Genetics; Utah)* | LCD: MolDX: Prostate Cancer Genomic Classifier Assay for Men with Localized Disease<br>• Testing performed in AK, ID, OR, WA, UT, AZ, MT, ND, SD, and WY: L38341<br>• Testing performed in CA and NV: L38339<br>• Testing performed in AL, GA, TN, SC, VA, WV, NC: L38292<br><br>**NOTES:**<br>• While the LCDs above specifically call out the *Decipher* test by name, they also state **other genomic tests may be eligible for coverage as well** if evaluated by the MolDX Program Contractor via the technical assessment (TA) process.<br>• Both the ***Oncotype DX® Genomic Prostate Score Assay*** and the ***Prolaris*** test by Myriad Genetics have completed this requirement and are listed as MolDX 'covered' tests in the DEX® Diagnostics Exchange registry. Thus, the criteria from the above LCDs also apply to these tests as indicated. |
| *Prostate Cancer Assays for* ***Risk Stratification***<br><br>***Examples include:***<br>*ConfirmMDx Epigenetic Molecular Assay (CPT 81551; MDxHealth; Irvine, California)*<br><br>*SelectMDx (MDxHealth; California) (0339U or CPT 81479 if prior to 10/1/2022)* | LCD: MolDX: Molecular Biomarkers to Risk-Stratify Patients at Increased Risk for Prostate Cancer (L39005)<br><br>**NOTES:**<br>• ***ConfirmMDx*** is listed as a potentially covered test in the companion LCA A58718 when the member meets the rest of the LCD criteria.<br>• ***SelectMDx*** has completed the required technical assessment [TA] review called out in the LCD and is listed as a MolDX "covered" test in the DEX® Diagnostics Exchange Registry. |

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| *PCA3 Testing (CPT 81313)*<br><br>*Includes the Progensa® PCA3 Assay (MetaMark Genetics; Massachusetts or Georgia)*<br><br>*MyProstateScore 2.0 (LynxDX; Ann Arbor, MI) (CPT 0403U)* (***As of 9/11/2024***) | For the Pregensa® test, apply the following:<br>• Testing performed in the states of VA, WV, NC, SC, GA, TN, AL: LCD for MolDX: Molecular Biomarkers to Risk-Stratify Patients at Increased Risk for Prostate Cancer (L38985) *(For Progensa®, use this coverage criteria for testing performed in either location. This test is listed as a potentially covered test in the companion LCA A58724 when the member meets the rest of the LCD criteria.)*<br><br>For PCA3 testing in general that is **not** specifically the Pregensa® test, as well as the MyProstateScore 2.0 test, apply the following (as appropriate for testing location):<br>• Testing performed in the states of IL, MN, WI, CT, NY, ME, MA, NH, RI, VT: LCD for Molecular Pathology Procedures (L35000) *(See criteria for PCA3 testing within the LCD, which is the same criteria for CPT 81313 in LCA A56199)*<br>• Testing performed in AK, ID, OR, WA, UT, AZ, MT, ND, SD, and WY: LCD for MolDX: Molecular Biomarkers to Risk-Stratify Patients at Increased Risk for Prostate Cancer (L39007)<br>• Testing performed in CA and NV: LCD for MolDX: Molecular Biomarkers to Risk-Stratify Patients at Increased Risk for Prostate Cancer (L39005)<br>• Testing performed in IA, KS, MO, NE, IN, and MI: MolDX: Molecular Biomarkers to Risk-Stratify Patients at Increased Risk for Prostate Cancer (L39042) |
| *Oncotype DX® AR-V7 Nucleus Detect Test (CPT 81479; California)* | LCD: MolDX: Phenotypic Biomarker Detection from Circulating Tumor Cells (L38643) (The LCD requires successful completion of TA review of the test; this test meets this LCD requirement.) |
| *ProMark Risk Score (CPT 81479; MetaMark Genetics; Massachusetts or Georgia)* | LCD: MolDX: ProMark Risk Score (L36665) *(Use this LCD for testing performed in either location)* |
| *ExoDx prostate (also known as ExosomeDx®, EPI, or IntelliScore) (Exosome Diagnostics; Massachusetts) (CPT 0005U)*<br><br>*Prostate Health Index (PHI or phi) (Beckman Coulter)* | **Prior to 3/1/2024:** LCD: Biomarker Testing (Prior to Initial Biopsy) for Prostate Cancer Diagnosis (L37733)<br><br>**On/after 3/1/2024:** These tests may be considered **medically necessary** when ordered by a physician or other qualified health care professional for the treatment of prostate cancer. It is expected that the ordering provider is familiar with the proper parameters of use of each test that they may be ordering. *(Source is LCA: Billing and Coding: Biomarker Testing for Prostate Cancer Diagnosis, A56609)* |
| *miR Sentinel™ Prostate Cancer Test (miR Scientific, LLC., New Jersey) (CPT 0343U, 0424U)* | Novitas LCA: Billing and Coding: Genetic Testing for Oncology (A59125) *(Code 0343U is included in the "non-covered" list of codes. 0424U was a new code for this test as of 1/1/2024 – apply same non-coverage logic for 0343U to 0424U.)* |

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| *UroSeq® Hereditary DNA Repair Panel (Theranostix, Inc. D/B/A Strand Diagnostics; Indiana)*<br><br>*ProstateNext®*<br><br>*ProstateNext® +RNAinsight™ (This is considered a combination test and may be considered medically necessary when reported with a single code and when LCD criteria are met)*<br><br>*ProstateNow™ Prostate Germline Panel (CPT 0475U) (GoPath Diagnostics, Inc.; Illinois and Arizona)* | LCD: MolDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer<br>• Testing performed in IA, KS, MO, NE, IN, and MI: L39040<br>• Testing performed in AK, ID, OR, WA, UT, AZ, MT, ND, SD, and WY: L38974<br>• Testing performed in CA and NV: L38972<br><br>**NOTES:**<br>• All of the above LCDs requires successful completion of TA review of the test; all of these tests **meet** this LCD requirement.<br>• While the UroSeq® test may be eligible for coverage, the *know error®* system for specimen validity that may also be performed with the UroSeq® is **not** considered medically necessary according to LCA A55172, even if requested in connection to the UroSeq® test. Separate coverage or reimbursement will not be allowed for the *know error®* system.<br>• The ProstateNow™ Prostate Germline Panel test is not FDA approved or cleared as companion diagnostic (CDx) test, so NCD 90.2 would not apply (tests without FDA clearance are subject to local MAC discretion). However, this test is listed as in the DEX® Registry under GoPath Diagnostics as "Covered," under both an Arizona and Illinois location. While the MAC over Illinois (National Government Services) does not use MoDX outcomes, the MAC over Arizona (Noridian J-F) does, and since coverage is potentially favorable for this latter service area using MolDX guidelines, we will use the noted Arizona LCD for this test, for testing in **any** location. |
| *IsoPSA® (Cleveland Diagnostics, Inc.; Ohio) (CPT 0359U)* | LCD: Prostate Cancer Detection with IsoPSA® (L39284) |
| *RNAinsight™ for ProstateNext® (Ambry Genetics; California) (CPT 0133U)*<br><br>*NeoLAB Prostate Liquid Biopsy (NeoGenomics Laboratories, Inc.; California) (CPT 0011M)*<br><br>*Apifiny® Score (Armune BioScience, Inc.; Michigan) (CPT 0021U)*<br><br>*Mi-Prostate score (also known as Michigan Prostate Score or* | The Medicare contractors (MACs) with jurisdiction over laboratories in these service areas have adopted guidelines developed and published by the Molecular Diagnostic Services (MolDX) Program for coverage decision making. As called out within relevant LCDs for these service areas (L36256, L35160, L35025, L36807, L36021), genetic and molecular tests performed within a MolDX service area are required to undergo a technical assessment (TA) review by the MolDX Medicare Contractor, Palmetto GBA. These TA reviews assess clinical utility and analytical validity (CU/AV) to ensure the tests meets requirements for Medicare coverage. The outcome of these TA reviews is maintained in the DEX™ Diagnostics Exchange registry catalog. These tests are **not medically necessary** because as of the date of the most recent policy review, these tests do **not** meet these LCD requirements.<br><br>*See "Policy Guidelines" below.* |

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| *MIPS) (MLabs; Michigan) (CPT 0113U)*<br><br>*MyProstateScore 2.0 (LynxDX; Ann Arbor, MI) (CPT 0403U) (**Prior to** 9/11/2024)*<br><br>*Stockholm3 (CPT 0495U) (BioAgilytix Diagnostics; North Carolina)*<br><br>*OncoAssure™ Prostate (CPT 0497U) (DiaCarta, Inc.; California)*<br><br>*PROSTOX™ ultra (CPT 0534U) (MiraDx, Inc.; California)* | NOTE: RNAinsight™ for ProstateNext®: According to direct communication from MolDX, this code is considered a stand-alone test and is **non-covered**. |
| **Medicare Coverage Criteria:** "MA organizations may create publicly accessible internal coverage criteria… when coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs." *(§ 422.101(b)(6) – see Policy Guidelines below*)<br>• **Medicare Coverage Manuals:** Medicare does not have criteria for the prostate tests listed below in a coverage manual.<br>• **National Coverage Determination (NCD):** Medicare does not have an NCD for the prostate tests below.<br>• **Noridian J-F Local Coverage Determination (LCD)/Local Coverage Article (LCA):** As of the most recent policy review, no Medicare Administrative Contractors (MACs) have LCDs for **PanGIA Prostate or EpiScore**.<br>• Therefore, in the absence of established Medicare coverage criteria in a manual, NCD, LCD, or other regulatory guidance for the health plan's service area, Company criteria below are applied for medical necessity decision-making. | |
| *PanGIA Prostate (CPT 0228U) (Genetics Institute of America, Florida)*<br><br>*EpiScore*<br><br>*ClarityDx Prostate (CPT 0550U) (Protean BioDiagnostics, Florida)* | Company medical policy for Protein Biomarker and Genetic Testing for the Prostate<br><br>I. These services are considered **not medically necessary** for Medicare based on the Company medical policy. *See Policy Guidelines below.* |

**IMPORTANT NOTICE:** While some services or items may appear medically indicated for an individual, they may also be a direct exclusion of Medicare or the member's benefit plan. Such excluded services or items by Medicare and member EOCs include, but are not limited to, services or procedures considered to be cosmetic, not medical in nature, or those considered not medically reasonable or necessary under *Title XVIII of the Social Security Act, §1862(a)(1)(A).* If there is uncertainty regarding coverage of a service or item, please review the member EOC or submit a pre-service organization

determination request. Note that the Medicare Advance Beneficiary Notice of Noncoverage (ABN) form **cannot** be used for Medicare Advantage members. *(Medicare Advance Written Notices of Non-coverage. MLN006266 May 2021)*

## POLICY CROSS REFERENCES

None

**The full Company portfolio of Medicare Medical Policies is available online and can be accessed here.**

## POLICY GUIDELINES

**DIAGNOSTIC LABORATORY TEST JURISDICTION**

The Company policy *PHA Medicare Medical Policy Development and Application* (MP# 50) describes the Plan's hierarchy with respect to Medicare medical policy development. In compliance with Medicare guidelines, some LCDs and LCAs used may be for test service areas **outside** of the Company service area. This is because Medicare's general rule regarding jurisdiction of claims furnished by an independent laboratory is that jurisdiction lies with the A/B MAC (B) (aka, Medicare Contractor) serving the **area in which the laboratory test is performed**.[1]

However, there may be exceptions to this rule. According to Medicare, while jurisdiction for laboratory services normally lies with the carrier serving the performing laboratory service area, there are situations where a regional or national lab chain jurisdiction (e.g., Quest Diagnostics, LabCorp, etc.) lies with a single carrier.[8] Therefore, tests performed by a national laboratory chain may have a single carrier established within the Company medical policies for all laboratory services they perform, regardless of the individual laboratory location. This allows for consistent outcomes for all members who receive the same test by the same lab chain.

Another exception to this rule involves "referring laboratory tests." This is when one laboratory sends the sample to another laboratory for processing. Under Medicare rules for referred tests, the location of the billing provider determines jurisdiction for claim payment and coverage criteria. Note that also under Medicare rules, only one laboratory is allowed to bill for the services rendered. If the performing laboratory and billing provider both submit a claim, then the performing laboratory's claim is the claim that would adjudicate according to member benefit.[10-12]

**Medicare's Molecular Diagnostic (MolDX) Program Contractor**

While many Medicare contractors (MACs) have adopted guidelines developed and published by the Molecular Diagnostic Services (MolDX) Program for their service areas, the program is **not** national in scope. MolDX-related reference materials only apply to genetic and molecular tests performed in the following states: OR, WA, AK, ID, UT, AZ, MT, ND, SD, WY, CA, NV, HI, NC, SC, AL, GA, TN, VA, WV, KY, OH, IA, KS, MO, NE, IN, and MI.[3]

The MolDX Program was developed by Palmetto GBA in 2011. The MolDX Contractor performs the following functions[3,4]:

- Establish clinical utility expectations.
- Complete technical assessments of published test data to determine clinical utility and coverage of individual tests.
- Develop unique test identifiers (Z-codes), adding to the DEX™ register of molecular diagnostic tests to allow for automated claims processing and to track utilization.
- Establish reimbursement.

**Table 1: General MolDX Requirements by LCD**

Genetic tests performed within a MolDX service area are required to undergo a technical assessment (TA) review by the MolDX Medicare Contractor, Palmetto. The LCDs in Table 1 detail this requirement:

| | LOCATION/MEDICARE CONTRACTOR | | | | |
|---|---|---|---|---|---|
| | ***NORIDIAN J-F***<br><br>OR, WA, AK, ID, UT, AZ, MT, ND, SD, and WY | ***NORIDIAN J-E***<br><br>CA and NV | ***PALMETTO GBA J-J AND J-M***<br><br>NC, SC, AL, GA, TN, VA, and WV | ***WPS J-5 AND J-8***<br><br>IA, KS, MO, NE, IN, and MI | ***CGS J-15***<br><br>KY and OH |
| **General MolDX Requirements** | L36256 | L35160 | L35025 | L36807 | L36021 |

**Note**: This list was accurate at the time of publication, but it is subject to change at any time by the Medicare MolDX Program contractor.

The outcome of these TA reviews is maintained in the DEX™ Diagnostics Exchange registry catalog and when possible, the coverage outcome is included within this medical policy to assist with coverage decision-making.

- Tests listed as "not covered" in this catalog have had clinical utility and analytical validity (CU/AV) reviewed and were determined to be **not medically reasonable or necessary** for Medicare under *Social Security Act, §1862(a)(1)(A)*.
- Tests which have **not yet** completed the required TA review are by default also considered to be **not medically reasonable or necessary** for Medicare under *§1862(a)(1)(A)*, based on the requirements found in the LCDs noted in Table 1 above.
- Tests listed as "covered" in this catalog have completed the required TA review and have been determined to be **medically reasonable or necessary** for Medicare under *§1862(a)(1)(A)*; however, this coverage is not automatic, as both of the following must be met:
    - Applicable NCD, LCD, and LCA criteria are met; and,
    - The member has signs/symptoms of a relevant disease or condition.

If a test is not specifically called out in this medical policy, additional research is required to determine coverage.

**Table 2: Tests relevant to this policy include the following**

*This list only applies to tests which do not have an LCD or LCA specific to that individual test in the Medicare guideline table above. This list was accurate at the time of publication, but it is subject to change at any time by the Medicare MolDX Program contractor. A "MolDX TA Review Outcome" of "Covered" does not indicate the test is automatically covered. All relevant criteria from the above Medicare references as applicable to the individual test must still be met.*

| Proprietary Test Name | Laboratory | MolDX TA Review Outcome (as found in the DEX™ Diagnostics Exchange registry) |
|---|---|---|
| **SelectMDx (CPT 0339U)** | MDxHealth; Irvine (California) | Covered (As of 2/17/2023) |
| **NeoLAB Prostate Liquid Biopsy (CPT 0011M)** | NeoGenomics Laboratories, Inc. (California) | Not covered *(No TA review noted in registry as of most recent policy review date)* |
| **Apifiny® Score (CPT 0021U)** | Armune BioScience, Inc. (Michigan) | Not covered *(No TA review in registry as of most recent policy review date)* |
| **Mi-Prostate score (also known as Michigan Prostate Score or MIPS) (CPT 0113U)** | MLabs (Michigan) | Not covered *(No TA review noted in registry as of most recent policy review date)* |
| **UroSeq® Hereditary DNA Repair Panel** | Strand Diagnostics (Indiana) | Not covered (As of 6/1/2023) |
| **Oncotype DX® AR-V7 Nucleus Detect Test** | Epic Sciences (California) | Covered |
| **Oncotype DX® Genomic Prostate Score Assay** | Exact Sciences (California) | Covered (As of 11/8/2020) |
| **RNAinsight™ for ProstateNext® (CPT 0133U)** ***(This is for RNAinsight™ as*** *its own separately billed* ***add-on test. This is*** *different* ***from the ProstateNext + RNAInsight™ billed as a single combined test, which is "covered" as of 9/9/2020)*** | Ambry Genetics (California) | Not covered |
| **IsoPSA® (CPT 0349U)** | Cleveland Diagnostics, Inc. (Ohio) | Not covered |
| **MyProstateScore 2.0 (CPT 0403U)** | LynxDX (Ann Arbor, MI) | Covered (As of 9/11/2024) |
| **ProstateNext®** | Ambry Genetics (California) | Covered (As of 2/26/2018) |
| **ProstateNext® +RNAinsight™** | Ambry Genetics (California) | Covered (As of 9/9/2020) |
| **ProstateNow™ Prostate Germline Panel (0475U)** | GoPath Diagnostics, Inc. (locations in both Illinois and Arizona) | Covered (As of 10/5/2023) |
| **Stockholm3 (0495U)** | BioAgilytix Diagnostics (North Carolina) | Not covered *(No TA review noted in registry as of most recent policy review date)* |
| **OncoAssure™ Prostate (CPT 0497U)** | DiaCarta, Inc. (California) | Not covered |
| **PROSTOX™ ultra (CPT 0534U)** | MiraDx, Inc. (California) | Not covered (As of 10/5/2022) |

Test coverage or non-coverage positions included in this medical policy were accurate at the time of policy publication, but they are subject to change by the Medicare MolDX Program contractor at any

time. Appeals to dispute non-coverage should include documentation by the MolDX Contractor which reflects a positive coverage decision (e.g., copy of the MolDX determination letter).

Summary

Many Medicare contractors (MACs) have adopted guidelines developed and published by the Molecular Diagnostic Services (MolDX) Program for their service area. As called out within relevant LCDs for these service areas (L36256, L35160, L35025, L36807, L36021), genetic and molecular tests performed within a MolDX service area are required to undergo a technical assessment (TA) review by the MolDX Medicare Contractor, Palmetto GBA. These TA reviews assess clinical utility and analytical validity (CU/AV) to ensure the tests meets requirements for Medicare coverage. The outcome of these TA reviews is maintained in the DEX™ Diagnostics Exchange registry catalog. When possible, the coverage outcome is included within this medical policy to assist with coverage decision-making.

- Tests listed as "not covered" in this registry have had the CU/AV reviewed and were determined to be not medically reasonable or necessary for Medicare under *Social Security Act, §1862(a)(1)(A).*
- Tests not listed at all have not yet completed the required TA review are by default also considered to be not medically reasonable or necessary for Medicare under §1862(a)(1)(A), based on the requirements found in the LCDs noted above.
- Tests listed as "covered" in this registry have completed the required TA review and have been determined to be potentially medically reasonable or necessary for Medicare under *§1862(a)(1)(A)*; however, applicable NCD, LCD, and LCA criteria must still be met, and the member must have signs/symptoms of a relevant disease or condition.

**Non-MolDX Service Area Genetic Testing**

Services areas which have **not** adopted MolDX guidelines include testing performed in the following states: FL, CO, NM, OK, TX, AR, LA, MS, DE, MD, NJ, PA, IL, MN, WI, CT, NY, ME, MA, NH, RI, and VT.

**Table 3: Non-MolDX Service Area LCDs**

The LCDs in Table 3 provide general coverage requirements for each jurisdiction area:

| STATE(S) | MEDICARE CONTRACTOR | LCD | COVERAGE REQUIREMENTS |
|---|---|---|---|
| **IL, MN, WI, CT, NY, ME, MA, NH, RI, and VT** | ***National Government Services (NGS) J-6 and J-K*** | L35000 | This LCD requires clinical utility and analytical validity be established, but it doesn't address all tests by name specifically. For panels, this LCD also states, "testing would be covered ONLY for the number of genes or test that are reasonable and necessary to obtain necessary information for therapeutic decision making."<br><br>In the absence of specific guidance in this LCD, the PHP Company policies for genetic tests provide a peer review of medical literature to evaluate clinical utility/analytical validity. When the biomarkers included in a test do not have proven clinical validity/utility, the test is not |

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| | | | medically reasonable or necessary under *Social Security Act, §1862(a)(1)(A)* for Medicare members. |
| **CO, NM, OK, TX, AR, LA, MI, DE, MD, NJ, and PA** | ***Novitas J-H and J-L*** | L35062 / L35396 | The LCD L35062 requires clinical utility and analytical validity be established, but it doesn't address all tests by name specifically. Additionally, for multi-biomarker panel test, the LCD L35396 requires evidence to support how "each requested biomarker can be individually contributory."<br><br>In the absence of specific guidance in these LCDs, the PHP Company policies for genetic tests provide a peer review of medical literature to evaluate clinical utility/analytical validity. When the biomarkers included in a test do not have proven clinical validity/utility, the test is not medically reasonable or necessary under *Social Security Act, §1862(a)(1)(A)* for Medicare members. |
| **FL** | ***First Coast Service Options J-N*** | L34519 | The LCD L34519 requires tests to undergo evaluation to establish clinical utility and analytical validity, based on published peer reviewed medical literature, or be FDA-approved, in order to be eligible for coverage. However, it doesn't address all tests by name specifically. For panels, this LCD also states, "testing would be covered ONLY for the number of genes or test that are reasonable and necessary to establish a diagnosis."<br><br>In the absence of specific guidance in this LCD, the PHP Company policies for genetic tests provide a peer review of medical literature to evaluate clinical utility/analytical validity. When the biomarkers included in a test do not have proven clinical validity/utility, the test is not medically reasonable or necessary under *Social Security Act, §1862(a)(1)(A)* for Medicare members. |

Only medically reasonable and necessary services or items which treat illness or injury are eligible for Medicare coverage, as outlined in *Title XVIII of the Social Security Act, §1862(a)(1)(A)*. As noted in Table 3, all of the listed LCDs require tests undergo evaluation to establish clinical utility (CU) and analytical validity (AV) in order to be eligible for coverage. However, due to the large number of proprietary tests marketed and available, most genetic tests – particularly panel tests – are not specifically called out by name within an LCD or LCA, nor do LCDs or LCAs provide the outcome for the peer-reviewed CU/AV for most tests. MA organizations (MAOs) make medical necessity determinations based on coverage and benefit criteria, the member's unique personal medical history (e.g., diagnoses, conditions, functional status, co-morbidities, etc.), physician recommendations, and clinical notes, as well as involvement of a plan medical director, where appropriate. *(§ 422.101(c)(1))*

> "MA organizations may create publicly accessible internal coverage criteria that are based on current evidence in widely used treatment guidelines or clinical literature when coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs. Current, widely-used treatment guidelines are those developed by organizations representing clinical medical specialties, and refers to guidelines for the treatment of specific diseases or conditions. Acceptable clinical literature includes large, randomized controlled trials or

prospective cohort studies with clear results, published in a peer-reviewed journal, and specifically designed to answer the relevant clinical question, or large systematic reviews or meta-analyses summarizing the literature of the specific clinical question." *(§ 422.101(b)(6) and Medicare Managed Care Manual, Ch. 4, §90.5)*

The Company policy *PHA Medicare Medical Policy Development and Application* (MP# 50) describes the Plan's hierarchy with respect to Medicare medical policy development. Medicare rules and regulations state that when no NCD, LCD, LCA, or other Medicare coverage guideline exists, Medicare allows Medicare Advantage Organizations (MAOs) to make coverage determinations based on an objective, evidenced-based process.

**Table 4: Tests relevant to this policy include the following:**

*Note: This list was accurate at the time of publication, but it is subject to change at any time by a Medicare contractor.*

| Proprietary Test Name | Laboratory | Company Medical Policy Coverage Position |
|---|---|---|
| **EpiScore** | | Not Covered |
| **miR Sentinel™ Prostate Cancer Test (0343U, 0424U)** | miR Scientific, LLC | Not Covered |
| **PanGIA Prostate (CPT 0228U)** | Genetics Institute of America | Not Covered |
| **ClarityDx Prostate (CPT 0550U)** | Protean BioDiagnostics | Not Covered |

Summary

For service areas which have **not** adopted MolDX guidelines, their applicable LCDs (L35000, L35062 / L35396, L34519) also require that each test have established clinical utility and analytical validity (CU/AV) in order to be eligible for Medicare coverage. Due to the large number of proprietary tests marketed and available, most genetic tests are not specifically called out within an LCD or LCA, nor do LCDs or LCAs provide the outcome for the peer-reviewed CU/AV for most tests. For these service areas, the Plan uses an objective, evidenced-based process to make coverage determinations and the Company medical policy criteria is applied to tests not called out within an LCD directly. See the "Evidence Summary" from the Company Medical Policy for *Prostate: Protein Biomarkers and Genetic Testing* (MP96) for a detailed explanation.

While some tests have demonstrated value in patient management of prostate cancer, not all prostate biomarker or genetic tests meet medical necessity requirements. These non-covered tests include, but may not be limited to, the Prostate Cancer Risk Panel, PanGIA Prostate, EpiScore, and miR Sentinel™ Prostate Cancer Test. These tests are considered not medically reasonable or necessary under *Social Security Act, §1862(a)(1)(A)* for Medicare members.

**EpiSwitch® Prostate Screening Test**

The EpiSwitch Prostate Screening (PSE) test is a blood-based screening test for prostate cancer which can be administered alongside or following a standard PSA test. The test evaluates the PSA score plus a

targeted PCR evaluation of five DNA regulatory markers called chromatin-conformation signatures (CCS). Currently under Medicare, preventive benefits for prostate cancer screening are limited to a digital rectal exam or a screening prostate specific antigen (PSA) test. Prostate cancer screening services eligible for coverage can also be found in the member's evidence of coverage (EOC) benefit contract.

## REGULATORY STATUS

**U.S. FOOD & DRUG ADMINISTRATION (FDA)**

While clearance by the Food and Drug Administration (FDA) is a prerequisite for Medicare coverage, the 510(k) premarket clearance process does not in itself establish medical necessity. Medicare payment policy is determined by the interaction of numerous requirements, including but not limited to, the availability of a Medicare benefit category and other statutory requirements, coding and pricing guidelines, as well as national and local coverage determinations and clinical evidence.

## BILLING GUIDELINES AND CODING

**GENERAL**

For applicable billing guidelines, please see related local coverage articles (LCAs):

- LCA: Billing and Coding: MolDX: 4Kscore Assay (A57337)
- LCA: Billing and Coding: MolDX: Prostate Cancer Genomic Classifier Assay for Men with Localized Disease (A57236)
- LCA: Billing and Coding: MolDX: ConfirmMDx Epigenetic Molecular Assay (A57606)
- LCA: MolDX: Oncotype DX Genomic Prostate Score Coding and Billing Article (A56372)
- LCA: Billing and Coding: MolDX: Prostate Cancer Genomic Classifier Assay for Men with Localized Disease (A57236)
- LCA: Progensa® PCA3 Assay Billing and Coding guidelines (A54492)
- LCA: Billing and Coding: MolDX: ProMark Risk Score (A57609)
- LCA: Billing and Coding: Prostate Cancer Detection with IsoPSA™

A number of the assays addressed in the policy are to be billed with specific codes.

| Assay | Code |
|---|---|
| **4K score** | 81539 |
| **ConfirmMDx** | 81479, 81551 |
| **Decipher** | 81479, 81542 |
| **Genomic Prostate Score® (GPS) Test** | 81479, 0047U |
| **PCA3** | 81313 |
| **Prolaris** | 81479, 81541 |
| **ProMark** | 81479 |
| **NeoLAB™** | 0011M |
| **Mi-Prostate Score (MiPS)** | 0113U |
| **Apifiny®** | 0021U |

| | |
|---|---|
| **ExosomeDx® Prostate (IntelliScore)** | 0005U |
| **RNAinsight™ for ProstateNext®** | 0133U |
| **SelectMDx®** | 0339U |
| **miR Sentinel™ Prostate Cancer** | 0343U, 0424U |
| **IsoPSA®** | 0359U |
| **MyProstateScore 2.0** | 0403U |
| **ProstateNow™ Prostate Germline Panel** | 0475U |
| **Stockholm3** | 0495U |
| **OncoAssure™ Prostate** | 0497U |
| **PROSTOX™ ultra** | 0534U |
| **ClarityDx Prostate** | 0550U |

| **CODES*** | | |
|---|---|---|
| **CPT** | 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 *(Used to report the NeoLAB Prostate Liquid Biopsy by NeoGenomics Laboratories, Inc.)* |
| | 0005U | Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score *(Used to report the ExoDx Prostate test (also known as ExosomeDx®, EPI, or IntelliScore) by Exosome Diagnostics)* |
| | 0021U | Oncology (prostate), detection of 8 autoantibodies (ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2), *(Used to report the Apifiny® Score by Armune BioScience, Inc.)* |
| | 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 *(Used to report the Genomic Prostate Score® (GPS) Test by MDxHealth, Inc. Formerly known as the Oncotype DX Genomic Prostate Score, Genomic Health, Inc.)* |
| | ~~0053U~~ | **TERMED 6/30/2023**<br>~~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 *(Used to report the Mi-Prostate score (also known as Michigan Prostate Score or MIPS) test by MLabs)* |
| | 0133U | Hereditary prostate cancer–related disorders, targeted mRNA sequence analysis panel (11 genes) (List separately in addition to code for primary procedure) *(Used to report the RNAinsight™ for ProstateNext® by 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 *(Used to report the PanGIA Prostate test by Genetics Institute of America)* |

| | | |
|---|---|---|
| | 0339U | Oncology (prostate), mRNA expression profiling of HOXC6 and DLX1, reverse transcription polymerase chain reaction (RT-PCR), first-void urine following digital rectal examination, algorithm reported as probability of high-grade cancer *(Used to report the SelectMDx® for Prostate Cancer test by MDxHealth, Inc.)* |
| | 0343U | Oncology (prostate), exosome-based analysis of 442 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as molecular evidence of no-, low-, intermediate- or high-risk of prostate cancer *(Used to report the miR Sentinel™ Prostate Cancer Test by miR Scientific, LLC.)* |
| | 0359U | Oncology (prostate cancer), analysis of all prostate-specific antigen (PSA) structural isoforms by phase separation and immunoassay, plasma, algorithm reports risk of cancer *(Used to report the IsoPSA® test by Cleveland Diagnostics, Inc.)* |
| | 0403U | Oncology (prostate), mRNA, gene expression profiling of 18 genes, first-catch urine, algorithm reported as percentage of likelihood of detecting clinically significant prostate cancer *(Used to report the MyProstateScore 2.0 test by LynxDX)* |
| | 0424U | Oncology (prostate), exosome-based analysis of 53 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RTqPCR), urine, reported as no molecular evidence, low-, moderate- or elevated-risk of prostate cancer *(Used to report the miR Sentinel™ Prostate Cancer test by miR Scientific®, LLC)* |
| | 0433U | Oncology (prostate), 5 DNA regulatory markers by quantitative PCR, whole blood, algorithm, including prostate-specific antigen, reported as likelihood of cancer *(Used to report the EpiSwitch® Prostate Screening (PSE) test by Oxford BioDynamics Inc.)* |
| | 0475U | Hereditary prostate cancer-related disorders, genomic sequence analysis panel using next-generation sequencing (NGS), Sanger sequencing, multiplex ligation-dependent probe amplification (MLPA), and array comparative genomic hybridization (CGH), evaluation of 23 genes and duplications/deletions when indicated, pathologic mutations reported with a genetic risk score for prostate cancer *(Used to report the ProstateNow™ Prostate Germline Panel test by GoPath Diagnostics, Inc.)* |
| | 0495U | Oncology (prostate), analysis of circulating plasma proteins (tPSA, fPSA, KLK2, PSP94, and GDF15), germline polygenic risk score (60 variants), clinical information (age, family history of prostate cancer, prior negative prostate biopsy), algorithm reported as risk of likelihood of detecting clinically significant prostate cancer *(Used to report the Stockholm3 test by BioAgilytix Diagnostics)* |
| | 0497U | Oncology (prostate), mRNA gene-expression profiling by real-time RT-PCR of 6 genes (FOXM1, MCM3, MTUS1, TTC21B, ALAS1, and PPP2CA), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a risk score for prostate cancer *(Used to report the OncoAssure™ Prostate test, by DiaCarta, Inc.)* |
| | 0534U | Oncology (prostate), microRNA, single-nucleotide polymorphisms (SNPs) analysis by RT-PCR of 32 variants, using buccal swab algorithm reported as a risk score *(Used to report the PROSTOX™ ultra test, by MiraDx, Inc.)* |
| | 0550U | Oncology (prostate), enzyme-linked immunosorbent assays (ELISA) for total prostate-specific antigen (PSA) and free PSA, serum, combined with age, previous negative prostate biopsy status, digital rectal examination findings, prostate volume, and image and data reporting of the prostate, algorithm reported as a risk score for the presence of high-grade prostate cancer *(Used to report the ClarityDx Prostate test, by Protean BioDiagnostics)* |

| | | |
|---|---|---|
| | 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 |
| | 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 |
| | 81599 | Unlisted multianalyte assay with algorithmic analysis |
| | 84999 | Unlisted chemistry code |
| **HCPCS** | None | |

***Coding Notes:**

- The code list above is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit. According to Medicare, "presence of a payment amount in the MPFS and the Medicare physician fee schedule database (MPFSDB) does not imply that CMS has determined that the service may be covered by Medicare." The issuance of a CPT or HCPCS code or the provision of a payment or fee amount by Medicare does **not** make a procedure medically reasonable or necessary or a covered benefit by Medicare. *(Medicare Claims Processing Manual, Chapter 23 - Fee Schedule Administration and Coding Requirements, §30 - Services Paid Under the Medicare Physician's Fee Schedule, A. Physician's Services)*
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

## *REFERENCES*


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2. Medicare Program Integrity Manual, Chapter 13 – Local Coverage Determinations, §13.5.4 - Reasonable and Necessary Provision in an LCD; Available at: https://www.cms.gov/Regulationsand-Guidance/Guidance/Manuals/Downloads/pim83c13.pdf [Cited 02/16/2024]
3. Palmetto GBA MolDX Manual; Available at: https://www.palmettogba.com/Palmetto/moldx.Nsf/files/MolDX_Manual.pdf/$File/MolDX_Manual.pdf?Open& [Cited 02/16/2024]

4. Healthcare Fraud Prevention Partnership (HFPP) White Paper for Genetic Testing Fraud, Waste, and Abuse; Available at: https://www.cms.gov/hfpp/hfpp-white-papers [Cited 02/16/2024]
5. Noridian web page for Molecular Diagnostic Services (MolDX); Last Updated: 9/23/2021; Available at: https://med.noridianmedicare.com/web/jfb/policies/moldx
6. Medicare Managed Care Manual, Ch. 4 - Benefits and Beneficiary Protections, §90.4.1 - MACS with Exclusive Jurisdiction over a Medicare Item or Service; Available at:
7. https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/mc86c04.pdf
8. Medicare Claims Processing Manual, Chapter 1 - General Billing Requirements, §10.1.5.4 - Independent Laboratories; Available at: https://www.cms.gov/Regulations-andGuidance/Guidance/Manuals/Downloads/clm104c01.pdf
9. Noridian LCA for Billing and Coding: MolDX: Targeted and Comprehensive Genomic Profile Next-Generation Sequencing Testing in Cancer (A56518); Available at: https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=56518
10. Medicare Claims Processing Manual, Ch. 1 - General Billing Requirements, §10.1.5.4.1 – Cases Involving Referral Laboratory Services; Available at: https://www.cms.gov/Regulations-andGuidance/Guidance/Manuals/Downloads/clm104c01.pdf
11. Medicare Claims Processing Manual, Chapter 16 - Laboratory Services, §40.1 – Laboratories Billing for Referred Tests; Available at: https://www.cms.gov/regulations-andguidance/guidance/manuals/downloads/clm104c16.pdf
12. Medicare Claims Processing Manual, Chapter 16 - Laboratory Services, §50.5.1 - Jurisdiction Of Referral Laboratory Services; Available at: https://www.cms.gov/regulations-andguidance/guidance/manuals/downloads/clm104c16.pdf

## *POLICY REVISION HISTORY*

| DATE | REVISION SUMMARY |
|---|---|
| 1/2023 | Q1 2023 code updates (converted to new format 2/2023) |
| 6/2023 | Annual review. Moved 0228U from a different policy to this policy |
| 10/2023 | Q4 2023 code updates |
| 1/2024 | Interim update to SelectMDx test criteria and Q1 2024 code updates |
| 5/2024 | Annual review. Update to 4Kscore Assay, miR Sentinel™ Prostate Cancer and IsoPSA® test criteria; update title |
| 7/2024 | Q3 2024 code updates |
| 9/2024 | Interim update; add new LCD for prostate gene expression tests, effective September 2024 |
| 10/2024 | Interim update and Q4 2024 code updates; update to EPI and Prostate Health Index (PHI or phi) test criteria |
| 1/2025 | Interim update; clarify LCD criteria for localized disease |
| 3/2025 | Interim update; update to MyProstate Score 2.0 (MPS 2.0) test criteria |