

LCD - MoIDX: Molecular Biomarkers to Risk-Stratify Patients at Increased Risk for Prostate Cancer (L39007)

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Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATES
Noridian Healthcare Solutions, LLC	A and B MAC	02101 - MAC A	J - F	Alaska
Noridian Healthcare Solutions, LLC	A and B MAC	02102 - MAC B	J - F	Alaska
Noridian Healthcare Solutions, LLC	A and B MAC	02201 - MAC A	J - F	Idaho
Noridian Healthcare Solutions, LLC	A and B MAC	02202 - MAC B	J - F	Idaho
Noridian Healthcare Solutions, LLC	A and B MAC	02301 - MAC A	J - F	Oregon
Noridian Healthcare Solutions, LLC	A and B MAC	02302 - MAC B	J - F	Oregon
Noridian Healthcare Solutions, LLC	A and B MAC	02401 - MAC A	J - F	Washington
Noridian Healthcare Solutions, LLC	A and B MAC	02402 - MAC B	J - F	Washington
Noridian Healthcare Solutions, LLC	A and B MAC	03101 - MAC A	J - F	Arizona
Noridian Healthcare Solutions, LLC	A and B MAC	03102 - MAC B	J - F	Arizona
Noridian Healthcare Solutions, LLC	A and B MAC	03201 - MAC A	J - F	Montana
Noridian Healthcare Solutions, LLC	A and B MAC	03202 - MAC B	J - F	Montana
Noridian Healthcare Solutions, LLC	A and B MAC	03301 - MAC A	J - F	North Dakota
Noridian Healthcare Solutions, LLC	A and B MAC	03302 - MAC B	J - F	North Dakota
Noridian Healthcare Solutions, LLC	A and B MAC	03401 - MAC A	J - F	South Dakota
Noridian Healthcare Solutions, LLC	A and B MAC	03402 - MAC B	J - F	South Dakota
Noridian Healthcare Solutions, LLC	A and B MAC	03501 - MAC A	J - F	Utah
Noridian Healthcare Solutions, LLC	A and B MAC	03502 - MAC B	J - F	Utah
Noridian Healthcare Solutions, LLC	A and B MAC	03601 - MAC A	J - F	Wyoming
Noridian Healthcare Solutions, LLC	A and B MAC	03602 - MAC B	J - F	Wyoming

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MolDX: Molecular Biomarkers to Risk-Stratify Patients at Increased Risk for Prostate Cancer

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N/A

Source Proposed LCD

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Issue

Issue Description

This LCD outlines limited coverage for this service with specific details under **Coverage Indications, Limitations and/or Medical Necessity**.

Issue - Explanation of Change Between Proposed LCD and Final LCD

The proposed LCD was modified for clarification and to include provisions regarding the performance of the biomarker tests (within scope of the policy) in exceptional circumstances.

CMS National Coverage Policy

Title XVIII of the Social Security Act, §1862(a)(1)(A) allows coverage and payment for only those services that are considered to be reasonable and necessary.

42 CFR 410.32(a) Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions.

CMS Internet-Only Manual, Pub. 100-02, Medicare Benefit Policy Manual, Chapter 15, §80 Requirements for Diagnostic X-Ray, Diagnostic Laboratory, and Other Diagnostic Tests §80.1.1 Certification Changes

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Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

There are two applications of molecular biomarkers to risk-stratify patients at increased risk for prostate cancer:

- I. A non-invasive or minimally invasive test, the results of which are obtained to inform the decision to perform an initial biopsy pre-biopsy.
- II. A test performed to further refine risk when a biopsy has been performed but does not clearly indicate malignancy on histopathologic examination (post-biopsy). Such a test can potentially obviate the need for a repeat biopsy.

This contractor provides limited coverage for molecular Deoxyribonucleic acid/ribonucleic acid (DNA/RNA) biomarker tests for the diagnosis of prostate cancer that help differentiate men who may or may not benefit from a prostate biopsy when ALL of the following conditions are met:

1. The patient must not have an established diagnosis of prostate cancer.
2. The beneficiary is a candidate for prostate biopsy or repeat prostate biopsy, according to a consensus guideline [(i.e., National Comprehensive Cancer Network® (NCCN), American Society of Clinical Oncology®(ASCO), American Urological Association (AUA)].
 - a. For men \leq 75 years of age - Prostate Specific Antigen (PSA) (or adjusted PSA in special populations, i.e., patients taking 5alpha-reductase inhibitors) OR repeat PSA are >3 and <10 ng/mL AND/OR Digital Rectal Exam (DRE) findings are very suspicious for cancer.
 - b. For men $>$ 75 years of age - PSA (or adjusted PSA in special populations, i.e., patients taking 5-alpha-reductase inhibitors) OR repeat PSA are ≥ 4 and <10 ng/mL AND/OR DRE findings are very suspicious for cancer.

EXCEPTION: a molecular biomarker test may be performed in men with PSA levels >10 ng/mL who are being considered for repeat biopsy IF appropriate according to consensus guidelines AND according to the following: the specific biomarker test has been validated in men with PSA levels >10 ng/mL AND a Multiparametric MRI (mpMRI) is negative, *if performed*.

3. The beneficiary has not had a prostate biopsy OR has had a previous negative or non-malignant but abnormal histopathology finding (i.e., atypical small acinar proliferation (ASAP) or high-grade prostatic intraepithelial neoplasia (HGPIN) on prostate biopsy).
 - Patients under consideration for a repeat biopsy have first undergone repeat PSA and/or DRE testing as recommended by consensus guidelines
4. The beneficiary would benefit from treatment of prostate cancer and patient management will be impacted by use of a biomarker in a manner already demonstrated in the peer-reviewed published literature to improve patient outcomes.
5. The medical record supports the medical necessity for the biomarker test.
6. Testing is performed according to the intended use of the test in the intended patient population for which the test was developed and validated.
7. Testing must be performed according to Clinical Laboratory Improvement Amendments (CLIA) and/or Food and Drug Administration (FDA) regulations in an accredited laboratory.
8. For a given clinical indication (pre-OR post-biopsy), only one molecular biomarker may be performed UNLESS a

second test, meeting all the criteria established herein, is reasonable and necessary as an adjunct to the first test, according to criteria established in this policy.

9. 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.
10. The analytes measured have demonstrated clinical validity and clinical utility (i.e., improved detection or discrimination of cancer or high-grade cancer or reduction in the need for biopsy) in the peer-reviewed published literature, establishing a clear and significant biological/molecular basis for stratifying patients and subsequently selecting (either positively or negatively) their clinical management decision within a clearly defined population.
11. The 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 beneficiary and the ordering provider is located closer to the beneficiary's place of residence than the nearest specialist. We would generally expect that beneficiaries for whom the test is ordered under this exception to be living in rural locations, islands, or some other location where access to care is limited.

NOTE: If the patient is considered higher risk (due to relevant family or personal cancer history, relevant high-risk genetic mutations, African ancestry, or other clinical parameters highly suspicious for cancer including a persistent and significant increase in PSA), a biopsy may still be warranted. These relative indications for biopsy should be taken into consideration as part of a shared decision-making process regarding whether to proceed with a biopsy.

Analytical validity, clinical validity (of novel analytes), and clinical utility will be assessed as part of a thorough and comprehensive technical assessment (TA) by the Molecular Diagnostic Services Program (MoIDX®).

Summary of Evidence

Prostate cancer is the second leading cause of cancer deaths in American men. Estimates for 2020 have shown that over 191,000 men will be diagnosed in the United States.^{1,2} Prostate cancer can be an indolent, non-aggressive disease or a fast-growing, aggressive disease with significant morbidity and mortality. Prostate cancer guidelines, therefore, aim to limit unnecessary detection and invasive procedures for indolent disease while maximizing the detection and treatment of aggressive cancer.

Prostate cancer screening with the PSA level has been an accepted approach to screening men for prostate cancer, and it is a statutorily covered Medicare benefit. The PSA level correlates with the risk of prostate cancer and the higher above the median PSA (for a given age group), the higher the risk for prostate cancer and aggressive prostate cancer. Approximately 30% of men with serum PSA levels between 4 and 10 ng/mL will be found to have prostate cancer, and total PSA levels >10 ng/mL confer a >67% likelihood of prostate cancer.^{3,4} As such, NCCN guidelines recommend that patients with a PSA >10 ng/mL should be encouraged to undergo biopsy.⁴ However, PSA is not a cancer-specific marker, and it is widely known that PSA values can be elevated and fluctuate for a variety of reasons other than cancer including inflammation, infection, and benign prostate hyperplasia.^{5,6} While the test is sensitive, its negative predictive value (NPV) is relatively low and there are numerous false positives.^{7,8} A cohort study of 1268 patients found that repeating the PSA resulted in normal (<4 ng/mL) values for nearly 25% of patients with initial PSA levels between 4 and 10 ng/mL.⁶ Moreover, compared with men who had an abnormal repeat PSA result, men with normal repeat PSA results were less likely to undergo biopsy and were approximately 80% less likely to have a diagnosis of prostate cancer and Gleason score of 7 or higher.⁶ False negative PSA results also occur. In the Prostate Cancer Prevention Trial, 15% of men with PSA levels ≤4.0 ng/mL (and normal DREs) were diagnosed with prostate cancer; of these, 14.9% had a Gleason score of 7 or higher.⁹ Therefore, there is not one particular value or cut-off with sufficiently high sensitivity and specificity for assessing prostate cancer risk.

Given the suboptimal ability of the PSA to accurately assess prostate cancer risk, there is ambiguity regarding its clinical value at various levels when reviewing associated outcomes subsequent to screening.⁸ A large multi-center randomized controlled study, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, was conducted involving over 76,000 men from 55 to 74 years of age who received either annual PSA measurements and digital rectal examinations or their usual care.¹⁰ After 7 to 13 years of follow-up, the mortality rates were low in both groups and not significantly different.^{10,11} However, the study's control arm included opportunistic screening for prostate cancer and therefore greatly confounded the results. Another large trial involving 8 European countries, the European Randomized study of Screening for Prostate Cancer (ERSPC), randomized 182,160 men between the ages of 50 and 74 to receive either screening for prostate cancer including PSA measurements or a 'truer' control arm (in which only a relatively small number of men had previously taken a PSA test).¹² Patients received a prostate biopsy if there was a concern for cancer based on the screening data. This study subsequently followed patients for 16 years and found that the screening group had a significant relative reduction in prostate-cancer related mortality of 21% (reported at 13 years of follow-up) and an even larger absolute benefit and reduction in excess incidence with the longer follow-up time of 16 years.^{13,14}

Although PSA screening has been associated with a significant reduction in prostate-cancer related mortality, it has also led to the increased incidence of prostate cancer, resulting in the overdiagnosis and overtreatment of indolent tumors, considered to be clinically insignificant.^{12,15-18} Autopsy studies have shown that among 70-79 year old men, more than one-third to one-half have indolent prostate cancer that would not have caused harm if undiagnosed and untreated.¹⁸ The performance of prostate biopsies, an invasive intervention, is currently the next step in diagnosis and management, and can involve significant complications, including hospitalization in approximately 1% of patients.¹⁹ Moreover, prostate biopsy is also prone to challenges such as sampling error, which may further lead to both over- and under-treatment,²⁰ with the false-positive and complication rates from biopsy being higher in older men.⁷

The management of patients with prostate cancer may include active surveillance versus definitive therapy. From 1994 through 2002, a large study of men with localized prostate cancer diagnosed shortly after PSA screening randomized 731 subjects to radical prostatectomy vs observation. There was no significant difference in either prostate-cancer specific mortality or all-cause mortality through at least 12 years of follow-up.²¹ Although with longer follow-up, the mortality rate was lower in men who underwent prostatectomy, though this finding was not statistically significant.²² Additionally, urinary incontinence, erectile dysfunction (ED), and bowel incontinence were significantly more common among those men who underwent a prostatectomy.²² In spite of these challenges, prostate cancer deaths have decreased by 50% since 1988, in large part due to enhanced screening measures.^{2,23,24}

As a result of the ambiguous risk-benefit profile associated with prostate cancer screening and management, guidelines on screening have differed among national organizations over the years. In 2012, the United States Preventative Services Task Force (USPSTF) recommended against PSA-based screening for prostate cancer, in large part as a result of the initial PLCO and ERSPC reports.²⁵ However, their most recent update recommended that screening for prostate cancer with a PSA test should be an individualized decision for men (aged 55 to 69 years) to discuss with their physicians, but cautioned that there is a significant risk of false positives and overtreatment with the possibility of significant complications such as ED and incontinence.²⁶ Such guidance was similarly endorsed by the Choosing Wisely initiative, which also highlighted the American Urological Association's (AUA) recommendation to consider a PSA test only after talking with one's doctor about risk factors.^{27,28} Guidelines from the NCCN recommend PSA testing to screen for prostate cancer in men 45-75 years of age in average-risk patients (and 40-75 years of age in higher-risk patients) as a level 2A recommendation; testing men >75 years of age is only recommended in healthy men with few to no comorbidities and is a level 2B recommendation, as widespread testing in this age group would significantly increase rates of overdiagnosis.⁴ Moreover, NCCN guidelines recommend repeat testing if an abnormally high PSA is observed, particularly if the value is close to the threshold value that prompts evaluation.⁴ In the case of a prior negative biopsy, the guidelines recommend repeat PSA and DRE at 6- to 24-month intervals with consideration of repeat biopsy based on results.

It is evident that not all prostate cancers are the same, and detection and treatment should focus specifically on prostate cancers that are more likely to contribute to morbidity and mortality. It is also evident that there are challenges with PSA testing, and a PSA-based screening strategy has not been proven to help differentiate low risk from aggressive prostate cancer. First-generation PSA derivative assays (e.g., free PSA, complexed PSA) were designed to increase PSA specificity for prostate cancer, but not necessarily specificity for clinically significant cancer. Additionally, multiparametric MRI (mpMRI) significantly increases the detection of clinically significant, higher-risk disease and is recommended for many patients with elevated PSA levels being considered for initial and repeat biopsy. However, a negative MRI does not exclude the possibility of cancer.^{4,30} As such, there is clinical utility for diagnostic tests that can better refine the implications of an elevated PSA test to help distinguish men with potentially life-threatening cancer from men who have indolent prostate cancer or no prostate cancer.

Biomarkers

The most current NCCN recommendations reflect the growing body of evidence supporting the use of prostate biomarkers to further identify, and risk stratify those patients at risk of high-grade prostate cancer requiring further management from those with low grade or indolent cancer who might not benefit from further intervention and who may be spared unnecessary biopsies and interventions. Such biomarkers are non-invasive (typically blood-or urine-based) and may contribute to improved sensitivity and specificity of screening, surpassing the limitations of PSA testing.^{4,31-33}

There are numerous biomarker tests available for biopsy-naïve patients that may improve the detection of prostate cancer or higher-grade prostate cancer. Some of these are non-molecular (i.e., they do not detect DNA and/or RNA), and include the percent free PSA (%fPSA), 4Kscore, and Prostate Health Index (PHI). Free PSA (fPSA) is an unbound form of PSA that is FDA approved for use in men with normal DRE and PSA levels of 4-10 ng/mL. At a cutoff of 25% in men with PSA values between 4–10ng/mL, fPSA has been shown to detect the majority of prostate cancers while avoiding approximately 20% of unnecessary biopsies.³⁴ The 4Kscore[®] measures kallikrein markers (including PSA and fPSA) in the blood and considers other clinical parameters such as age and DRE, which together have been reported to better detect clinically significant cancer.³⁵⁻³⁹ Finally, the Prostate Health Index (PHI) is a blood-based immunoassay that uses PSA, fPSA, and p2PSA (an isoform of fPSA) to calculate a score that categorizes a patient's risk as low, moderate, or high. Studies have shown that the PHI improves the sensitivity of prostate cancer detection,^{43,44} discriminates high-grade cancer^{43,45} and can reduce the rate of prostate biopsies.⁴⁶

Other pre-biopsy biomarker tests are molecular and measure the expression of genes or epigenetic changes associated with prostate cancer. Some of these couple gene expression with other clinical and laboratory parameters in multimodal models, to optimize their clinical performance.⁴⁷⁻⁵¹ For example, SelectMDx[®] evaluates messenger ribonucleic acid (mRNA) levels of HOXC6 and DLX1 relative to Kallikrein-related Peptidase 3 (KLK3). When combined with additional clinical risk factors in a multimodal approach, prospective multicenter studies found that the area under the curve (AUC) of the receiver operating characteristic (ROC) reached 0.90 in predicting detection of high-grade prostate cancer; importantly, the risk score remained a strong predictor (AUC 0.78) in men with PSA levels <10 ng/mL.⁵² A urine exosome gene expression assay, the ExoDx[™] Prostate IntelliScore (EPI), has also been reported to be statistically more predictive than standard of care (SOC) alone for predicting Gleason score of 7 (GS 7) prostate cancer from GS 6 and benign disease.⁵⁰ A clinical utility study in men scheduled for initial biopsy found that, at a cutoff of 15.6, the test had a NPV of 89% and would reduce total biopsies by 20%; however, the test would miss 7% of high grade cancers.⁴⁹ In men with a prior negative biopsy, a prospective clinical validation study found that the EPI test had a NPV of 92% and would have avoided 26% of unnecessary biopsies while missing 2% of high-grade cancers.⁵³ Importantly, these results were independent of SOC and other clinical features.

In the post-biopsy setting, there are biomarkers that improve specificity in patients who have had at least 1 prior negative biopsy. Some of these are liquid biomarkers that overlap with those already discussed for use in biopsy-naïve patients, while others are tissue-based and should only be performed on a biopsy specimen. Some utilize gene expression data while others evaluate epigenetic markers such as hypermethylation in select genes thought to be associated with aggressive disease.⁵⁴⁻⁵⁷ Progenisa[®] PCA3 is an mRNA expression assay that can be tested from post-DRE urine. In the post-biopsy setting, it has been shown to improve the specificity of prostate cancer detection and determine which patients should undergo a repeat biopsy. One multi-center study evaluating men with at least 1 prior negative prostate biopsy reported that those with a score of <25 were more than 4 times as likely to have a negative repeat biopsy as men with a score of ≥25.⁵⁸ ConfirmMDx[®] is a multi-gene test that uses prostate biopsy tissue to assess the methylation status of 3 biomarkers (GSTP1, RASSF1, APC) associated with prostate cancer.^{54,57} The performance of this assay in large, blinded clinical validation studies demonstrated a NPV of 90% for all prostate cancer and 96% for high-grade disease, considerably higher than that afforded by standard histopathology review.^{54,56} A field observation study conducted in 138 patients with negative biopsies found a repeat biopsy rate of 4.3%,⁵⁹ significantly lower than the 40% repeat biopsy rate reported in the PLCO trial, for patients with an initial negative biopsy.⁶⁰

In summary, use of biomarker tests may help overcome the limitations of screening by PSA as well as the limitations and risks associated with prostate biopsy. On the whole, use of these biomarker tests can better detect cancer or high-grade cancer, and can reduce the performance of unnecessary prostate biopsies and their associated risks. It should be noted that mpMRI is also a consideration in these same patients and, though data is emerging that combining biomarkers with mpMRI results in improved diagnostic accuracy, it is not yet known how biomarker tests can be optimally used in conjunction with MRI.

Analysis of Evidence (Rationale for Determination)

Numerous prior Medicare coverage decisions have considered the evidence in the hierarchical framework of Fryback and Thornbury⁶¹ where Level 2 addresses diagnostic accuracy, sensitivity, and specificity of the test; Level 3 focuses on whether the information produces change in the physician's diagnostic thinking; Level 4 concerns the effect on the patient management plan and Level 5 measures the effect of the diagnostic information on patient outcomes. To apply this same hierarchical framework to analyze an *in vitro* diagnostic test, we utilized the ACCE Model Process for Evaluating Genetic Tests.⁶² The practical value of a diagnostic test can only be assessed by taking into account subsequent health outcomes. When a proven, well-established association or pathway is available, intermediate health outcomes may also be considered. For example, if a particular diagnostic test result can be shown to change patient management and other evidence has demonstrated that those patient management changes improve health outcomes, then those separate sources of evidence may be sufficient to demonstrate positive health outcomes from the diagnostic test.

Screening for prostate cancer using PSA is a statutorily covered benefit. However, PSA is a screening test, and is not diagnostic of either prostate cancer or of prostate cancer requiring immediate intervention. The diagnosis relies on a prostate biopsy, which is associated with a risk of significant post-operative complications.

NCCN Guidelines recognize the benefits of improving the identification of significant cancer while avoiding the detection of indolent disease, and recommend (as a level 2A recommendation) the consideration of a biomarker test (one that has been validated in peer-reviewed studies) to better define the probability of higher-grade cancer (Gleason score 3+4, Grade Group 2 or higher) in patients who meet PSA standards for consideration of prostate biopsy.⁴ For patients who have not yet had a biopsy, the guidelines include the use of %fPSA to improve cancer

detection, and PHI, SelectMDx[®], 4Kscore[®], and ExoDx[™] Prostate (EPI) tests to further define the probability of higher-grade cancer.⁴ They also include %fPSA, PHI, 4Kscore[®], EPI, PCA3 and ConfirmMDx[®] to improve specificity for patients thought to be at higher risk despite a prior negative biopsy.⁴ However, as there is variation in the number and quality of clinical validity and clinical utility studies published, it is not always clear which biomarker test may be optimal in a particular setting.^{4,63}

A systematic review found that prostate biomarker tests, even when combined with a pre-existing multivariable clinical risk calculator such as the Prostate Cancer Prevention Trial (PCPT) or the European Randomized Screening for Prostate Cancer (EPSRC) risk calculator, can still miss 5% to 10% of clinically significant cancers.⁶⁴ The authors concluded that “Incorporating the newer prostate biomarkers and mpMRI into predictive algorithms like the PCPT and EPSRC risk calculators is likely necessary when deciding whether a patient can forego prostate biopsy.”⁶⁴ They also caution against using biomarker tests in a binary fashion and note that urologists will need to decide how to use these tests to determine probability of cancer within the context of the pre-existing risk predictors, the patient’s ethnicity, life expectancy and quality-of-life goals, and cost.⁶⁴ Similarly, the NCCN guidelines state that no biomarker test can be recommended over any other at this time and that the optimal order of combining biomarker tests with imaging is unknown.⁴ Moreover, questions remain regarding how to interpret results of multiple tests in individual patients, particularly when results are contradictory. The guidelines also do not recommend the use of a single parameter (such as a risk calculator) to determine whether a biopsy is indicated; rather, they encourage a multi-faceted approach that includes clinical judgment and patient preferences. They also cite several recent studies suggesting that biomarker testing performed in parallel with conditional MRI may be an efficient and effective way to assess those with a persistently elevated PSA. As such, they caution that biomarker tests can be complex and should be interpreted carefully, and with referral to a specialist.⁴

Finally, as some biomarker tests are not clinically validated in patients with PSA levels >10 ng/mL, their performance in this population is unknown.⁴ Moreover, though the patients being considered for repeat biopsy of the prostate may have a rising PSA above this level, the threshold for repeat biopsy should also be significantly lower in this group, as “patients with a persistent and significant increase in PSA should be encouraged to undergo biopsy.”⁴

In sum, biomarkers can help stratify men who have an elevated PSA into those more likely versus less likely to have aggressive disease. These non-invasive biomarker tests have demonstrated that they can (1) reduce the need for unnecessary biopsies in men unlikely to have prostate cancer or high-grade prostate cancer and/or (2) better define men at risk for higher-grade prostate cancer. There is adequate evidence to show that the incremental information provided by validated molecular biomarker tests for prostate cancer in samples of patients whose findings can be generalized to the Medicare population, changes physician management in a way that improves outcomes. Tests that fulfill all criteria outlined in this policy will similarly be considered for coverage.

The reference to specific biomarkers in this document does not imply coverage by MolDX[®]. Further, this policy is restricted in scope to molecular biomarkers only; therefore, non-molecular biomarkers for the same intended use, though not covered by this policy, may meet coverage criteria of other local coverage determinations.

This contractor will continue to evaluate biomarkers and will provide coverage based on the pertinent literature as well as professional society and nationally recognized guidelines (i.e., (NCCN)).

General Information

Associated Information

N/A

Sources of Information

N/A

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Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
07/27/2023	R1	Under CMS National Coverage Policy updated section headings. Under Bibliography revised Source #27 to remove broken hyperlink and changes were made to citation to reflect AMA citation guidelines. Formatting, punctuation and typographical errors were corrected throughout the LCD. Acronyms were inserted where appropriate throughout the LCD.	<ul style="list-style-type: none"> Provider Education/Guidance

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Articles

[A58724 - Billing and Coding: MoIDX: Molecular Biomarkers to Risk-Stratify Patients at Increased Risk for Prostate Cancer](#)

[A59144 - Response to Comments: MoIDX: Molecular Biomarkers to Risk-Stratify Patients at Increased Risk for Prostate Cancer](#)

LCDs

[DL39007 - \(MCD Archive Site\)](#)

Related National Coverage Documents

N/A

Public Versions

UPDATED ON	EFFECTIVE DATES	STATUS
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