Local Coverage Determination (LCD): MolDX: Oncotype DX AR-V7 Nucleus Detect for Men with Metastatic Castrate Resistant Prostate Cancer (MCRPC) (L37746)

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Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATE(S)
Noridian Healthcare Solutions, LLC	A and B MAC	01111 - MAC A	J - E	California - Entire State
Noridian Healthcare Solutions, LLC	A and B MAC	01112 - MAC B	J - E	California - Northern
Noridian Healthcare Solutions, LLC	A and B MAC	01182 - MAC B	J - E	California - Southern
Noridian Healthcare Solutions, LLC	A and B MAC	01211 - MAC A	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01212 - MAC B	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01311 - MAC A	J - E	Nevada
Noridian Healthcare Solutions, LLC	A and B MAC	01312 - MAC B	J - E	Nevada
Noridian Healthcare Solutions, LLC	A and B MAC	01911 - MAC A	J - E	American Samoa California - Entire State Guam Hawaii Nevada Northern Mariana Islands

LCD Information

Document Information

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LCD Title
MolDX: Oncotype DX AR-V7 Nucleus Detect for Men with Metastatic Castrate Resistant Prostate Cancer (MCRPC)

Proposed LCD in Comment Period
N/A

Source Proposed LCD
DL37746

AMA CPT / ADA CDT / AHA NUBC Copyright Statement

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CMS National Coverage Policy

Title XVIII of the Social Security Act (SSA), §1862(a)(1)(A), states that no Medicare payment shall be made for items or services that "are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."

Title XVIII of the Social Security Act, §1833(e), prohibits Medicare payment for any claim lacking the necessary documentation to process the claim.

42 Code of Federal Regulations (CFR) §410.32 Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions.

CMS Internet Online Manual Pub. 100-02 (Medicare Benefit Policy Manual), Chapter 15, Section 80, "Requirements for Diagnostic X-Ray, Diagnostic Laboratory, and Other Diagnostic Tests"

CMS Internet-Only Manuals, Publication 100-04, Medicare Claims Processing Manual, Chapter 16, §50.5 Jurisdiction of Laboratory Claims, 60.12 Independent Laboratory Specimen Drawing, 60.2. Travel Allowance.

CMS Internet Online Manual Pub. 100-04 (Medicare Claims Processing Manual), Chapter 23 (Section 10) "Reporting ICD Diagnosis and Procedure Codes"

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

This contractor will provide limited coverage for the Oncotype DX AR-V7 Nucleus Detect to help determine which patients with metastatic castrate resistant prostate cancer may benefit from androgen receptor signaling inhibitor therapy and which may benefit from chemotherapy.

Summary of Evidence

Men with metastatic castration resistant prostate cancer (mCRPC) have multiple life extending, FDA-approved therapeutics options. However, there is no clear consensus on the therapeutic sequencing after initial exposure to an androgen receptor signaling inhibitor (ARSi), such as apalutamide, abiraterone or enzalutamide. The response rate for a second ARSi, Abiraterone after Enzalutamide, or Enzalutamide after Abiraterone is lower than the initial exposure. Therefore, the most common clinical decision focuses on whether to start a second ARSi or taxane chemotherapy. It is therefore important to identify patients who will not respond to a 2nd ARSi in order to 1) avoid giving an ineffective therapy, and 2) delaying giving a more effective therapy, such as taxane chemotherapy, taxane combination therapies, Radium-223, PARP inhibitors, and platinum chemotherapy.

AR-V7 protein results from alternative androgen receptor (AR) mRNA splicing, which produces a constitutively active receptor that is associated with resistance to ARSi such as abiraterone and enzalutamide.[1,2] A growing body of evidence suggests that patients with AR-V7 positive mCRPC do not benefit from ARSi therapy but may respond to taxanes, such as docetaxel.[3-5] Supporting observations include that 1) AR-V7 positivity is associated with resistance to androgen receptor-targeted therapies[4]; 2) taxanes are equally effective in AR-V7–positive and AR-V7–negative mCRPC patients[3,5] ; and 3) AR-V7 status may change during therapy.[6] For these reasons, the National Comprehensive Cancer Network (NCCN) suggests that AR-V7 is a biomarker that may help guide therapy in mCRPC.[7]

AR signaling requires that the AR transcriptional elements bind to DNA within the nucleus of the cancer cell. Therefore, the nuclear localization of the AR-V7 truncated protein may improve the clinical specificity of predicting ARSi resistance.[8] Analysis of AR-V7 localization scoring guides has demonstrated that only nuclear AR-V7 protein expression improves the clinical specificity of predicting ARSi resistance, and importantly, is associated with improved overall survival with taxane chemotherapy.[9]

Oncotype DX® AR-V7 Nuclear Detect

Test Description and Intended Use

The *Oncotype* DX AR-V7 Nuclear Detect test is a commercially available, circulating tumor cell (CTC) based, liquid biopsy test. The test detects patients with CTCs who have nuclear expression of the AR-V7 truncated protein and provides information that can help guide treatment selection in patients with mCRPC.

Test Performance

The AR-V7 assay is run on the Epic CTC platform (Figure 2). The procedures used for the AR-V7 assay and Epic CTC platform, including pre-analytical and analytical processes, have been in place since 2008 in our research laboratory and since 2015 in our clinical laboratory. As required by US federal (Clinical Laboratory Improvement Amendments [CLIA]) and state laboratory regulations, alternative proficiency testing (a blinded assessment of assay performance), consistent with CLIA regulations is regularly performed by our laboratory and has documented the consistency and reproducibility of the assay. The methodology for the AR-V7 assay yields precise and highly reproducible results.

Clinical Validation

The *Oncotype* DX AR-V7 Nuclear Detect test has been clinically validated with 191 mCRPC samples representing 161 unique patients. Patients whose samples had nuclear AR-V7 positive CTCs before ARSi therapy had resistant post-therapy PSA changes, shorter rPFS (median, 2.3 vs 14.5 months; P<.001), shorter time on therapy (median, 2.1 vs 6.8 months; P<.001), and shorter OS (median, 4.6 months vs. not reached; P<.001) than those without nuclear AR-V7 positive CTCs. A multivariable analysis adjusting for baseline factors associated with survival showed superior OS with taxanes relative to ARS inhibitors when AR-V7 positive CTCs were detected pre-therapy (hazard ratio, 0.24; 95% CI, 0.10-0.57; P=0.035).

Summary of Analytical and Clinical Performance

General

Intended Use	1. Patients with progressive, metastatic castration-resistant prostate cancer, (mCRPC) as defined by the Prostate Cancer Working Group 2 guidelines (a minimum of 2 rising prostate-specific antigen (PSA) levels 1 or more weeks

	apart, new lesions by bone scintigraphy, and/or new or enlarging soft tissue lesions by computed tomography (CT) or magnetic resonance imaging (MRI)) 2. Patients who have failed one androgen receptor signaling (ARS) inhibitor, specifically Enzalutamide (Xtandi) or Abiraterone (Zytiga) 3. Patients who are considered appropriate for treatment by their treating physician for the alternative ARS inhibitor (ARSi), specifically Enzalutamide (Xtandi) or Abiraterone (Zytiga), as a single agent.
Validated Specimen Type(s)	Peripheral blood collected in Streck Cell-Free DNA BCT tubes

Analytical Performance

Description	Results (with 95% Confidence Intervals if applicable) [1]
Intermediate precision 36 slides total: 12 slides (6 positive and 6 negative) on 3 non-consecutive days, by 3 different operators, using a different combination of critical AR-V7 detection reagents (i.e., three combinations of primary, Rabbit Anti-AR-V7 and secondary, Goat-Anti-Rabbit Horse Radish Peroxidase; 2 manufacturing lots each). One batch of test slides was scanned on two different imaging instruments.	100% (36/36; 90.3-100.0%)
Reproducibility (between sites)	N/A. All tests will be performed at a single site.
Minimum input quantity	1.7 mL whole blood collected in Streck Cell-Free DNA BCT tubes
Limit of blank (LOB)	DU145 control slides monitor background staining: Mean AR-V7 ratio (i.e., the intensity of AR-V7 signal in control cells divided by the background signal intensity across a slide) must be < 13 and no nuclear AR-V7+ cells should be observed.

Limit of detection (LOD)	**AR-V7 signal ratio:** An AR-V7 positive cell must have an AR-V7 ratio ≥ 3.2 in order for it to be distinguished as positive. **AR-V7 positive cells:** Each AR-V7 test analyzes at least 1.7 mL of blood, enabling the detection of two positive cells per mL of blood with over 95% confidence.
Limits of quantitation (LOQ)	N/A. The AR-V7 test is a qualitative test reported as positive or negative.
Linearity	Total positive cell numbers are not reported in test results. The test result is binary, reporting negative, if no positive cells are found; and, positive, if one or more positive cell(s) is/are found.
Interfering substances	The presence of endothelial cells and lipids, to a concentration of 2.6% v/v (equivalent to blood triglyceride level of over 1000 mg/dL) were demonstrated to have no effect on assay performance. Gross hemolysis of blood specimen can impact clinical sensitivity of the test and is a criterion for not processing a sample.
Specimen stability, primary	The stability of whole blood in the collection tube was evaluated positive and negative laboratory derived, tested over six time points (0, 8, 24, 48, 72, 96 h). The test results were analyzed for a negative and positive result. Additional acceptance criteria for positive samples included maintaining targeted cell spike-in number and incidence of nuclear localized AR-V7 signal (>81%). All results demonstrated acceptable primary sample stability up to the 72hr timepoint. Samples older than 72h will not be processed.
Specimen stability, intermediate	N/A; samples are lysed upon receipt and immediately fixed prior to staining
Critical reagent closed/shelf-life stability	Critical reagents include Pan CK (C-11+PCK-26+CY-90+KS-1A3+M20+A53-B/A2); CK19 (RCK108); CD45:Alexa647 (F10-89-4); AR-V7 antibody (EPR15656); Goat α-Mouse-IgG1/CF555-conjugated; GARHRP; and 488-Tyramide and AMP buffer. Shelf-life stability determined by manufacturer.
Critical reagent open/in use stability	All critical reagents are single use only. Testing demonstrates on-board stability over ~5-hour run.

[1] Using Clopper-Pearson method

Clinical Performance: Validity (Scher et al. 2016 JAMA Oncology)

Prognostic value of AR-V7 positivity on ARSi therapy by endpoint:

Endpoint	Hazard Ratio: AR-V7(+) vs. (-)	p-value
Time on ARSi	4.13	< 0.0001
rPFS	3.7	0.0002
Overall Survival	11.45 (5.67-23.82)	< 0.001

AR-V7: Therapy Interaction: Multivariable Cox PH Model

	Comparison	Hazard Ratio (95% CI)
AR-V7 Status & Therapy	AR-V7(+): Taxane vs AR	0.242 (0.103 to 0.569)
	AR-V7(-): Taxane vs AR	0.924 (0.440 to 1.946)

Analysis of Evidence
(Rationale for Determination)

Level of Evidence

Quality of Evidence: Moderate
Strength of Evidence: Moderate
Weight of Evidence: Limited

Criteria for Coverage

Oncotype DX AR-V7 Nuclear Detect assay is covered as follows:

1. Patients will have progressive mCRPC as defined by the Prostate Cancer Working Group 2 guidelines (a minimum of 2 rising prostate-specific antigen (PSA) levels 1 or more weeks apart, new lesions by bone scintigraphy, and/or new or enlarging soft tissue lesions by computed tomography (CT) or magnetic resonance imaging (MRI)).
2. Patients will have failed one ARSi, specifically Enzalutamide (Xtandi), Apalutamide (Erleada), or Abiraterone (Zytiga).
3. Patients will be considered appropriate for treatment by their treating physician for the alternative ARSi as a single agent.
4. Circulating tumor cells (CTC) with nuclear expression of AR-V7 protein will be assessed prior to initiation of therapy.
5. Decision impact analysis: We expect that < 15% of nuclear AR-V7-positive patients will receive an ARSi.
6. Efficacy analysis: Nuclear AR-V7-negative patients who receive an ARSi will have similar or better time on therapy than untested mCRPC patients (meeting above criteria) receiving ARSi.

Coding Information

Bill Type Codes:

Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type.Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.

N/A

Revenue Codes:

Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory. Unless specified in the policy, services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

N/A

CPT/HCPCS Codes

Group 1 Paragraph:

N/A

Group 1 Codes:

CODE	DESCRIPTION
81479	UNLISTED MOLECULAR PATHOLOGY PROCEDURE

ICD-10 Codes that Support Medical Necessity

Group 1 Paragraph:

N/A

Group 1 Codes:

ICD-10 CODE	DESCRIPTION
C61	Malignant neoplasm of prostate
C77.8	Secondary and unspecified malignant neoplasm of lymph nodes of multiple regions
C77.9	Secondary and unspecified malignant neoplasm of lymph node, unspecified
C78.00	Secondary malignant neoplasm of unspecified lung
C78.1	Secondary malignant neoplasm of mediastinum
C78.2	Secondary malignant neoplasm of pleura
C78.30	Secondary malignant neoplasm of unspecified respiratory organ
C78.4	Secondary malignant neoplasm of small intestine
C78.5	Secondary malignant neoplasm of large intestine and rectum
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C78.80	Secondary malignant neoplasm of unspecified digestive organ
C78.89	Secondary malignant neoplasm of other digestive organs
C79.10	Secondary malignant neoplasm of unspecified urinary organs
C79.11	Secondary malignant neoplasm of bladder
C79.19	Secondary malignant neoplasm of other urinary organs
C79.31	Secondary malignant neoplasm of brain
C79.32	Secondary malignant neoplasm of cerebral meninges
C79.40	Secondary malignant neoplasm of unspecified part of nervous system

ICD-10 CODE	DESCRIPTION
C79.49	Secondary malignant neoplasm of other parts of nervous system
C79.51	Secondary malignant neoplasm of bone
C79.52	Secondary malignant neoplasm of bone marrow
C79.60	Secondary malignant neoplasm of unspecified ovary
C79.61	Secondary malignant neoplasm of right ovary
C79.62	Secondary malignant neoplasm of left ovary
C79.70	Secondary malignant neoplasm of unspecified adrenal gland
C79.71	Secondary malignant neoplasm of right adrenal gland
C79.72	Secondary malignant neoplasm of left adrenal gland
C79.81	Secondary malignant neoplasm of breast
C79.82	Secondary malignant neoplasm of genital organs
C79.89	Secondary malignant neoplasm of other specified sites
C79.9	Secondary malignant neoplasm of unspecified site
Z19.2	Hormone resistant malignancy status
Z85.46	Personal history of malignant neoplasm of prostate

ICD-10 Codes that DO NOT Support Medical Necessity

N/A

Additional ICD-10 Information

N/A

General Information

Associated Information

N/A

Sources of Information

N/A

Bibliography

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Revision History Information

N/A

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Article(s)
A56256 - Response to Comments: MolDX: Oncotype DX AR-V7 Nucleus Detect for Men with Metastatic Castrate Resistant Prostate Cancer (MCRPC)
LCD(s)
DL37746 - MolDX: Oncotype DX AR-V7 Nucleus Detect for Men with Metastatic Castrate Resistant Prostate Cancer (MCRPC)

Related National Coverage Documents

N/A

Public Version(s)

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