Local Coverage Determination (LCD):
MolDX: Oncotype DX AR-V7 Nucleus Detect for Men with Metastatic Castrate Resistant Prostate Cancer (MCRPC) (L37744)

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Contractor Information

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LCD Information

Document Information

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<td>L37744</td>
<td>For services performed on or after 03/02/2019</td>
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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**
DL37744

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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.”

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”

**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 2\textsuperscript{nd} 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.\textsuperscript{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.\textsuperscript{3-5} Supporting observations include that 1) AR-V7 positivity is associated with resistance
to androgen receptor-targeted therapies\textsuperscript{4}; 2) taxanes are equally effective in AR-V7–positive and AR-V7–negative
mCRPC patients\textsuperscript{3,5}; and 3) AR-V7 status may change during therapy.\textsuperscript{6} For these reasons, the National
Comprehensive Cancer Network (NCCN) suggests that AR-V7 is a biomarker that may help guide therapy in mCRPC.\textsuperscript{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.\textsuperscript{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.\textsuperscript{9}

**Oncotype DX® AR-V7 Nuclear Detect**

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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

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))

Intended Use

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

<table>
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<tr>
<th>Description</th>
<th>Results (with 95% Confidence Intervals if applicable)</th>
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<tbody>
<tr>
<td>Intermediate precision</td>
<td>100% (36/36; 90.3-100.0%)</td>
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<tr>
<td>Reproducibility (between sites)</td>
<td>N/A. All tests will be performed at a single site.</td>
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<tr>
<td>Minimum input quantity</td>
<td>1.7 mL whole blood collected in Streck Cell-Free DNA BCT tubes</td>
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<td>Limit of blank (LOB)</td>
<td>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 &lt; 13 and no nuclear AR-V7+ cells should be observed.</td>
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<tr>
<td>Limit of detection (LOD)</td>
<td><strong>AR-V7 signal ratio</strong>: An AR-V7 positive cell must have an AR-V7 ratio ≥ 3.2 in order for it to be distinguished as positive. <strong>AR-V7 positive cells</strong>: 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.</td>
</tr>
<tr>
<td>Limits of quantitation (LOQ)</td>
<td>N/A. The AR-V7 test is a qualitative test</td>
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reported as positive or negative.

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.

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.

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.

N/A; samples are lysed upon receipt and immediately fixed prior to staining.

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.

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:

<table>
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<tr>
<th>Endpoint</th>
<th>Hazard Ratio: AR-V7(+) vs. (-)</th>
<th>p-value</th>
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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**

<table>
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<th>Comparison</th>
<th>Hazard Ratio (95% CI)</th>
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<td>AR-V7(+) Taxane vs AR</td>
<td>0.242 (0.103 to 0.569)</td>
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<tr>
<td>AR-V7(-) Taxane vs AR</td>
<td>0.924 (0.440 to 1.946)</td>
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**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.

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**General Information**

**Associated Information**

N/A

**Sources of Information**

N/A

**Bibliography**


7. NCCN Clinical Practice Guidelines in Oncology- Prostate Cancer Version 2.2017


Revision History Information

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<th>REVISION HISTORY EXPLANATION</th>
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<td>12/01/2019</td>
<td>R3</td>
<td>The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD.</td>
<td>Other (The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD.)</td>
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<td>At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.</td>
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<td>12/01/2019: This LCD is being revised in order to adhere to CMS requirements per chapter 13, section 13.5.1 of the Program Integrity Manual. There has been no change in coverage with this LCD revision. Regulations regarding billing and coding were removed from the CMS National Coverage Policy section of this LCD and placed in the related Billing and Coding: MolDX: Oncotype DX AR-V7 Nucleus Detect for Men with Metastatic Castrate Resistant Prostate Cancer (MCRPC) A57499 Article.</td>
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<td>As required by CR 10901, all billing and coding information has been moved to the companion article, this article is linked to the LCD.</td>
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Associated Documents

Attachments
N/A

Related Local Coverage Documents
Article(s)
Related National Coverage Documents

N/A

Public Version(s)

Updated on 01/29/2020 with effective dates 12/01/2019 - N/A
Updated on 12/18/2019 with effective dates 12/01/2019 - N/A
Updated on 10/28/2019 with effective dates 12/01/2019 - N/A
Updated on 01/03/2019 with effective dates 03/02/2019 - N/A

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