

# Local Coverage Determination (LCD): MoIDX: Decipher® Biopsy Prostate Cancer Classifier Assay for Men with Intermediate Risk Disease (L38149)

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## Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATE(S)
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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
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## LCD Information

### Document Information

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L38149

**Original Effective Date**

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**LCD Title**

MoIDX: Decipher® Biopsy Prostate Cancer Classifier  
Assay for Men with Intermediate Risk Disease

**Proposed LCD in Comment Period**

N/A

**Source Proposed LCD**

DL38149

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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

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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.

## Coverage Guidance

### Coverage Indications, Limitations, and/or Medical Necessity

#### ≥Criteria for Coverage

The Decipher Biopsy is covered for men with prostate cancer only when the following clinical conditions are met:

- Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement), **and**
- FFPE prostate biopsy specimen with at least 0.5 mm of cancer length, and favorable or unfavorable intermediate risk disease as defined in the most recent available NCCN guideline 2018 V4, **and**
- Patient has an estimated life expectancy of greater than or equal to 10 years, **and**
- Patient is a candidate for definitive therapy (RP +/- PLND, EBRT + ADT, or EBRT + brachytherapy +/- ADT), **and**
- Result will be used to determine treatment among definitive therapy modalities or observation, **and**
- Patient has not received pelvic radiation or androgen deprivation therapy prior to the biopsy, **and**
- Patient is monitored for disease progression according to established standard of care

Variants of the Decipher Biopsy test including the genes / transcripts or algorithms are also covered for the above indications if those variations have analytical and clinical validity at least as good as the current Decipher Biopsy test. Validation documents will need to be reviewed by MoIDX to ensure that the modified test meets these requirements.

## Summary of Evidence

In 2017, over 160,000 new cases of prostate cancer were diagnosed, representing 9.6% of all new cancer diagnoses, and the second leading cause of cancer death in men (SEER).<sup>1</sup> Prostate cancer is the leading cause of cancer treatment-related years lived with disability worldwide, reflecting the confluence of its high incidence, long natural history, and treatment-associated morbidity.<sup>2</sup> Clinically localized prostate cancer accounts for ~80% of newly diagnosed cases.<sup>1</sup> The National Comprehensive Cancer Network (NCCN), classifies these men into risk groups based on clinical and pathological features, which are intended to be used in conjunction with life expectancy estimates to select optimal treatment approaches.<sup>3</sup> For men diagnosed with unfavorable intermediate risk disease and estimated to have at least 10 years of life expectancy, treatment is usually recommended in these guidelines (see Table 1 below).

Intermediate risk disease is a heterogeneous disease state of localized prostate cancer with a significant range of possible treatment intensities. The clinical approach to better risk stratify this patient cohort was the creation of favorable and unfavorable intermediate risk disease groups developed by Zumsteg and Spratt at Memorial Sloan Kettering, now adopted by NCCN guidelines (see PROS-2).<sup>4</sup>

**Table 1: NCCN 2018 V4 - Localized Prostate Cancer Risk Stratification and Treatment**

	<b>Very Low</b>	<b>Low</b>	<b>Risk Category Favorable Intermediate</b>	<b>Unfavorable Intermediate</b>	<b>High/Very High</b>
<b>Clinical/ pathologic features</b>	<ul style="list-style-type: none"> <li>• T1c <b>AND</b></li> <li>• Gleason score ≤6/grade group 1 <b>AND</b></li> <li>• PSA &lt;10 ng/mL <b>AND</b></li> <li>• Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core <b>AND</b></li> <li>• PSA density &lt;0.15 ng/mL/g</li> </ul>	<ul style="list-style-type: none"> <li>• T1-T2a <b>AND</b></li> <li>• Gleason score ≤6/grade group 1 <b>AND</b></li> <li>• PSA &lt;10 ng/mL</li> </ul>	<ul style="list-style-type: none"> <li>• T2b-T2c <b>OR</b></li> <li>• Gleason score 3+4=7/grade group 2 <b>OR</b></li> <li>• PSA 10-20 ng/mL</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Percentage of positive biopsy cores &lt;50%</li> </ul>	<ul style="list-style-type: none"> <li>• T2b-T2c <b>OR</b></li> <li>• Gleason score 3+4=7/grade group 2 or Gleason score 4+3=7/grade group 3 <b>OR</b></li> <li>• PSA 10-20 ng/mL</li> </ul>	<p><b>High:</b></p> <ul style="list-style-type: none"> <li>• T3a <b>OR</b></li> <li>• Gleason score 8/grade group 4 or Gleason score 4+5=9/grade group 5 <b>OR</b></li> <li>• PSA &gt;20 ng/mL</li> </ul> <p><b>Very high:</b></p> <ul style="list-style-type: none"> <li>• T3b-T4 <b>OR</b></li> <li>• Primary Gleason pattern 5 <b>OR</b></li> <li>• &gt;4 cores with Gleason score 8-10/grade group 4 or 5</li> </ul>
<b>Treatment Options</b>					
<b>≥20 y life expectancy</b>	<ul style="list-style-type: none"> <li>• Active surveillance</li> <li>• EBRT or brachytherapy</li> <li>• RP ± PLND (if predicted probability of lymph node metastasis ≥ 2%)</li> </ul>				
<b>≥10 y life expectancy</b>	<ul style="list-style-type: none"> <li>• Active surveillance</li> </ul>	<ul style="list-style-type: none"> <li>• Active surveillance</li> <li>• EBRT or brachytherapy alone</li> </ul>	<ul style="list-style-type: none"> <li>• Active surveillance</li> <li>• EBRT or brachytherapy alone</li> </ul>	<ul style="list-style-type: none"> <li>• RP ± PLND (if predicted probability of lymph node metastasis ≥</li> </ul>	

		<ul style="list-style-type: none"> <li>• RP ± PLND (if predicted probability of lymph node metastasis ≥ 2%)</li> </ul>	<ul style="list-style-type: none"> <li>• RP ± PLND (if predicted probability of lymph node metastasis ≥ 2%)</li> </ul>	<ul style="list-style-type: none"> <li>• EBRT + ADT (4-6 mo)</li> <li>• EBRT + brachytherapy ± ADT (4-6 mo)</li> </ul>	
<b>&lt;10 y life expectancy</b>	<ul style="list-style-type: none"> <li>• Observation</li> </ul>	<ul style="list-style-type: none"> <li>• Observation</li> </ul>	<ul style="list-style-type: none"> <li>• EBRT or brachytherapy</li> <li>• Observation</li> </ul>	<ul style="list-style-type: none"> <li>• EBRT + brachytherapy ± ADT (4-6 mo)</li> <li>• Observation</li> </ul>	
<b>&gt;5 y life expectancy</b>					<ul style="list-style-type: none"> <li>• EBRT + ADT (2-3 y)</li> <li>• EBRT + brachytherapy + ADT (1-3 y)</li> <li>• RP + PLND</li> </ul>

**<sup>a</sup>Active surveillance recommended for patients with 10-20 years life expectancy**

**PSA – Prostate Specific Antigen; EBRT – External Beam Radiation Therapy; RP – Radical Prostatectomy; PLND – Pelvic Lymph Node Dissection; ADT – Androgen Deprivation Therapy**

The recommendation to treat intermediate risk men, particularly those with unfavorable intermediate risk disease (UF-I, any 4+3=7 prostate cancer, multiple intermediate risk features, or >50% of cores involved by prostate cancer), is based in part on Level I evidence (SPCG-4 randomized clinical trial) showing survival benefit from definitive therapy.<sup>5</sup> However, the intensity of treatment appropriate in this risk stratum remains ambiguous despite further stratification of the intermediate risk disease category. Prospective randomized clinical trials and retrospective series suggest that in addition to local control by surgery, radiation therapy in the form of external beam radiation, with or without hormonal therapy, with or without brachytherapy boost, and with or without hypofractionation could all be employed to successfully treat these men (ProtecT trial, CHHiP trial, EORTC 22991, and ASCENDE-RT trials).<sup>6-9</sup> While there remains a significant range of potentially appropriate treatment intensities, current clinical and pathologic variables are unable to reliably identify which patients can safely be on single modality therapy or receive multi-modality therapy.

The broad range of recommended interventions for intermediate risk men is reflective of the heterogeneous metastatic potential of disease classified as intermediate risk and the increased morbidity of intensified therapy.<sup>6,9-16</sup> In all cases, treatment intensification appears most appropriate in men that are at elevated risk of disease progression.<sup>17</sup> As such, a clinical tool that is able to enhance risk stratification would be expected to allow for more informed decisions regarding treatment selection.

In addition to risk stratification with clinical variables, NCCN guidelines recommend considering the use of a genomic

risk classifiers.<sup>3</sup>

## **Decipher® Biopsy Prostate Cancer Classifier Assay**

### **Test Description**

Decipher Biopsy is a clinical-grade whole-transcriptome assay, measuring the expression of over 1.4 million RNAs (from coding and non-coding genes). The assay is performed on formalin-fixed paraffin embedded (FFPE) prostate cancer tumor tissue from diagnostic biopsy needle cores. The assay results are reported as a genomic classifier (GC) score based on gene expression using a machine-learning algorithm. The molecular pathways represented include proliferation/cell death, invasion & metastasis, androgen signaling, immune activity & response, growth & differentiation, angiogenesis and metabolism functions.

The test can be used to further risk stratify patients within the stratum of Unfavorable Intermediate Risk Disease, providing both a continuous score and a categorization of that score into low, average, or high risk with associated probabilities of high grade disease, 5 year metastatic risk, and 10 year prostate cancer specific mortality.

### **Test Performance**

Six clinical studies of clinically localized prostate cancer patients who were potential candidates for definitive therapy demonstrate:

- In men with NCCN intermediate or high-risk prostate cancer who were treated with surgery or radiation, Decipher Biopsy was prospectively validated as a biopsy-based predictor of metastasis and prostate cancer-specific mortality thus, establishing the assay as a robust and independent measure of prostate cancer aggressiveness.
- Decipher Biopsy adds independent information beyond standard clinical and pathologic measures and assesses underlying biology from very small biopsy tumor volumes, while also addressing issues of biopsy under-sampling to predict disease aggressiveness.
- Men with NCCN intermediate or high risk prostate cancer and a Decipher Biopsy score of <0.45 have a low risk of developing metastasis and/or prostate cancer specific death at 10 years.
- The addition of the Decipher Biopsy risk scores with the NCCN risk groups clinical stratification enables identification of a larger population of low risk patients who may not require neoadjuvant hormone therapy and conversely a smaller subset of patients most at risk that require intensification with longer duration hormone therapy or clinical trials of novel agents.

### **Clinical Validation for Metastasis**

Six clinical validation studies demonstrate the high discrimination of Decipher Biopsy for predicting lymph node involvement or metastasis. Recently, a study led by investigators at the University of California San Francisco (Xu et al., 2018) confirmed the ability of Decipher Biopsy to predict metastatic lymph node involvement in a cohort of 91 NCCN intermediate and high risk disease patients. In multivariable analysis (MVA) adjusting for clinical risk factors, the study showed that for every 10% increase in Decipher score was associated with an approximate 33-35% increase in the odds of harboring lymph node involvement as assessed on subsequent <sup>68</sup>Ga-PSMA-11 PET scan.

Berlin et al.<sup>19</sup> (2018) investigated Decipher Biopsy in an intermediate risk prostate cancer cohort (n=121) treated uniformly with 78 Gy image-guided intensity-modulated radiotherapy but without use of any neoadjuvant or adjuvant hormone therapy or brachytherapy boost. The cohort consisted primarily of NCCN unfavorable intermediate

risk disease patients (72%), men who NCCN guidelines currently recommend receive hormone therapy for 4-6 months or brachytherapy ± hormone therapy for 4-6 months with their radiation treatment. Decipher reclassified 72% of the cohort as low genomic risk. Berlin et al. (2018) reported that Decipher Biopsy was a significant predictor of metastasis (HR, 2.05; 95% CI, 1.24-4.24;  $p=0.004$ ) in multivariable models adjusting for NCCN risk groups. Also, the authors demonstrated that Decipher Biopsy was significantly more accurate than existing NCCN clinical criteria to predict metastasis (Decipher AUC 0.86 vs NCCN AUC 0.54). Finally, the study showed a 0% 5-year cumulative incidence of metastasis in Decipher Biopsy low risk men but 14.3% in Decipher Biopsy high risk men.<sup>19</sup>

Spratt et al.<sup>20</sup> (2018) demonstrated how the combination of NCCN and Decipher risk groups using a simple summation method to create a novel clinical-genomic risk system can dramatically improve risk stratification for clinically localized prostate cancer patients. In the biopsy validation cohort ( $n=235$ ) consisting primarily of unfavorable intermediate (40%) and high (35%) risk patients, the clinical-genomic model had an AUC of 0.84 (95% CI, 0.61-0.93) compared to 0.74 (95% CI, 0.65-0.84) with CAPRA alone for prediction of metastasis at 10 years post definitive treatment. Compared with clinical-genomic low risk group, the hazard ratio for metastasis was 21.3 (95% CI, 2.8-2728;  $p<0.001$ ) and 62.5 (95% CI, 8.5-7970;  $p<0.001$ ) for clinical-genomic intermediate and high risk groups, respectively. In combination with NCCN, men with low clinical-genomic risk had 10-year cumulative incidence of metastasis of 0% compared to 25.9% and 55.2% for clinical-genomic intermediate and high risk groups, respectively ( $p<0.001$ ).<sup>20</sup>

Nguyen et al.<sup>21</sup> (2017a) studied the validity of Decipher Biopsy for predicting metastasis for men treated with definitive radiation (i.e., external beam radiation therapy and/or brachytherapy with 4-6 months of neoadjuvant ADT). The cohort ( $n=100$ ) consisted of NCCN intermediate (55%) and high (45%) risk group patients. In MVA, each 0.1 unit increase in Decipher Biopsy score was significantly associated with time to distant metastasis (HR, 1.37; 95% CI, 1.06-1.78,  $p=0.014$ ). Decipher Biopsy had a c-index of 0.76 (95% CI, 0.57-0.89) for predicting metastasis at 5 years post definitive radiation, greater than NCCN risk groups and CAPRA clinical risk model alone. Finally, the authors performed a sensitivity analysis and found in survival analysis that for patients with a Decipher Biopsy score  $<0.2$ , there were no metastatic events at 10 years post definitive radiation and suggested that these men may be candidates for de-intensification of therapy. Furthermore, the study showed Decipher Biopsy classified 26% of NCCN intermediate and high risk men to Decipher high risk with a resulting 19.5% 5-year cumulative incidence of metastasis compared to 6.3% for Decipher Biopsy low risk patients. The authors concluded that the Decipher Biopsy high risk men would be good candidates for more potent systemic therapies and further that a significant portion of men in this cohort perhaps were over-treated with hormone therapy.<sup>21</sup>

In a follow-on study led by the Dana-Farber group, Nguyen et al.<sup>22</sup> (2017b) further demonstrated the ability of Decipher Biopsy to predict metastasis after definitive therapy. The cohort consisted primarily of 54% NCCN intermediate and 32% NCCN high risk treated with either definitive surgery ( $n=105$ ) or radiation ( $n=130$ ). Decipher reclassified 60% of these patients to low genomic risk, 18% as intermediate and 23% classified as high risk. In MVA, Decipher Biopsy was a significant predictor of metastasis (HR, 1.39; 95% CI, 1.15-1.69;  $p=0.001$ ) after adjusting for NCCN risk groups. The c-index for predicting 5-year metastasis was 0.74 (95% CI, 0.63-0.83) for Decipher Biopsy, which was substantially better than 0.60 (95% CI, 0.50-0.69) for the CAPRA clinical risk model and 0.66 (95% CI, 0.53-0.77) for NCCN risk groups. In this study, the Decipher low risk group had favorable outcomes with 5-year metastasis rate of only 4.1% compared to 21.0% in those with Decipher high risk.<sup>22</sup>

Klein et al.<sup>23</sup> (2016) found similar performance of Decipher Biopsy for predicting short and long-term oncological outcomes when measured in tumor tissue from diagnostic biopsy as compared to their original study in RP tissue. In MVA, Decipher Biopsy was shown to be a significant predictor of metastasis (HR, 1.66; 95% CI, 1.09-2.55;  $p=0.01$ ) after adjusting for NCCN risk groups. Decipher Biopsy alone had an improved c-index for 10-year metastasis risk of 0.80 (95% CI, 0.63-0.94) compared to NCCN model alone (c-index, 0.75; 95% CI, 0.64-0.87). The c-index for Decipher Biopsy plus NCCN model was much higher at 0.88 (95% CI, 0.77-0.96). Additionally, Decipher Biopsy was a significant predictor of 5-year metastasis with c-index of 0.87 (95% CI, 0.76-0.97). Decipher Biopsy reclassified 48

% of intermediate clinical risk men as low genomic risk and none of these patients developed metastasis on study follow-up.<sup>23</sup>

### Clinical Validation for Prostate Cancer-Specific Mortality

Decipher Biopsy also validated as a significant predictor of prostate cancer-specific mortality. Using univariable analysis, Nguyen et al. (2017b) showed that Decipher Biopsy was a significant predictor of prostate cancer-specific mortality (HR, 1.57; 95% CI, 1.03–2.48; p=0.037). Decipher Biopsy risk group was associated with 10-year cumulative incidence of prostate cancer-specific mortality—0% in men with Decipher low risk vs. 9.4% in those with Decipher high risk.<sup>22</sup>

### Results

Ball Point	Description	MVA Effect Size (95% CI, p-value)		AUC (95% CI) <sup>a</sup>	
		Decipher <sup>b</sup>	Clinical Risk <sup>c</sup>	Decipher	Clinical Risk <sup>c</sup> + Decipher
Biochemical Failure	Berlin (2018) <i>Int J Radiat Oncol Biol Phys</i> N=121	HR 1.36 (1.09-1.71, p=0.007)	0.56 (0.43-0.66) [NCCN, 5yr]	0.78 (0.59-0.91) [5yr]	0.85 (0.73-1.00) <sup>e</sup> [5yr]
Metastasis	Xu (2018) <i>Eur Urol Oncol</i>	OR 1.33 (1.04-1.71, p=0.02)	NR	NR	NR
	Berlin (2018) <i>Int J Radiat Oncol Biol Phys</i> N=121	HR 2.05 (1.24-4.24, p=0.004)	0.54 (0.32-0.67) [NCCN, 5yr]	0.86 (0.79-0.94) [5yr]	0.89 (0.68-1.00) [5yr]
	Spratt (2018) <i>J Clin Onc</i> N= 235	HR 21.3 (2.8-2728, p<0.001) 62.5 (8.5-7970, p<0.001) <sup>h</sup> [CGRG Int, High ref: Low]	0.74 (0.65-0.84) [CAPRA, 10yr]	NR	0.84 (0.61-0.93) <sup>g</sup> [10yr]
	Nguyen (2017) <i>Prostate Cancer Prostatic Disease</i> N=100	HR 1.37 (1.06-1.78, p=0.014)	0.63 (0.40-0.78) [NCCN, 5yr]	0.76 (0.57-0.89) [5yr]	NR
	Nguyen (2017) <i>Eur Urol</i> N=235	HR 1.39 (1.15-1.69, p=0.001)	0.66 (0.53–0.77) [NCCN, 5yr]	0.74 (0.63-0.83) [5yr]	0.74 (0.66-0.82) <sup>e</sup> [5yr]

	Klein (2016) <i>Urology</i> N=57	HR 1.66 (1.09-2.55, p=0.01)	0.75 (0.64-0.87) [NCCN, 10yr]	0.80 (0.63-0.94) [10yr]	0.88 (0.77-0.96) [10yr]
	Klein (2016) <i>Urology</i> <sup>h</sup>	OR 1.93 (1.10-3.91, p=0.02)	NR	0.87 (0.76-0.97) [5 yr]	NR
Prostate Cancer-Specific Mortality	Nguyen (2017) <i>Eur Urol</i> N=235	HR 1.57 (1.03-2.48, p=0.037) <sup>j</sup>	NR	0.73 (0.54-0.85) <sup>d</sup> [10 yr]	NR

- *MVA = multivariable analysis; CI = confidence interval; HR = hazard ratio; OR = odds ratio; ref = reference group; NR = not reported; CGRG = Clinical Genomic Risk Groups.*
- *a Time is specified in square bracket if time-dependent AUC is reported.*
- *b Hazard ratios or odds ratios of Decipher were reported per 10% increase in score.*
- *c Clinical risk model (indicated in square bracket) selected was the best reported comparator (highest AUC).*
- *e AUCs of MVA models were corrected for optimism.*
- *f The end point reported was lymph node involvement defined as PSMA-avid pelvic nodal involvement.*
- *g The results reported are based on a clinical genomic point-based system that combines NCCN and Decipher risk groups.*
- *h The end point reported was metastasis within 5 years.*
- *i Univariable HR*

## Guideline Review

The NCCN Clinical Practice Guideline in Oncology for Prostate Cancer notes that molecular assays may be able to reduce the uncertainty about the risk of disease progression, but no tests have been studied with randomized controlled trials.

## Analysis of Evidence (Rationale for Determination)

### Level of Evidence

Quality of Evidence-Moderate  
Strength of Evidence-Moderate  
Weight of Evidence-Moderate

Treatment paradigms for men with prostate cancer have been developed, and they are based in part on assessing the risk of a patient having an unfavorable outcome due to prostate cancer within the patient's expected lifetime. Patients at a higher risk are recommended to have a greater intensity of treatment. Within the unfavorable intermediate risk stratum, ambiguity regarding the optimal treatment approach remains. While there are no randomized controlled trials of outcomes using the Decipher Biopsy test, numerous studies from different institutions have all had similar and consistent findings, providing evidence that this test accurately risk stratifies patients. While research has not definitively shown that such risk-stratification improves outcomes in terms of either better prostate cancer outcomes or overall reductions treatment-related adverse events, there is sufficient evidence that this test is able to better inform patient and clinician decisions that must presently be made in a state of significant uncertainty. As such, this test provides clinically actionable incremental information that fits into existing evidence-based or

consensus-recommended prostate cancer treatment paradigms.

Since this test helps inform clinicians at a decision point regarding treatment intensity in the existing consensus treatment guidelines, the clinical utility of this test hinges on both the framework's treatment recommendations, and a certain level of decision uncertainty that accompanies treatment decisions within this framework. As such, this contractor will continue to monitor evidence and consensus recommendations regarding optimal selection of treatment intensity, and coverage may be re-evaluated following any substantial new evidentiary developments or guideline changes regarding the treatment of patients who are currently considered to have unfavorable intermediate risk prostate cancer. Such changes may include a new treatment paradigm or the development of a risk-stratification tool for which high quality, strength, and weight evidence shows improved outcomes and obviates the need for previously developed tests.

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## General Information

### Associated Information

N/A

### Sources of Information

N/A

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## Revision History Information

N/A

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## Associated Documents

### Attachments

N/A

### Related Local Coverage Documents

Article(s)

A57963 - Billing and Coding: MoIDX: Decipher® Biopsy Prostate Cancer Classifier Assay for Men with Intermediate Risk Disease

A57989 - Response to Comments: MoIDX: Decipher® Biopsy Prostate Cancer Classifier Assay for Men with Intermediate Risk Disease

LCD(s)

DL38149 - MoIDX: Decipher® Biopsy Prostate Cancer Classifier Assay for Men with Unfavorable Intermediate Risk Disease

**Related National Coverage Documents**

N/A

**Public Version(s)**

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## **Keywords**

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