

# Local Coverage Determination (LCD): MoIDX: DecisionDx-UM (Uveal Melanoma) (L37070)

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## Contractor Information

Contractor Name	Contract Type	Contract Number	Jurisdiction	State(s)
<a href="#">Noridian Healthcare Solutions, LLC</a>	A and B MAC	01111 - MAC A	J - E	California - Entire State
<a href="#">Noridian Healthcare Solutions, LLC</a>	A and B MAC	01112 - MAC B	J - E	California - Northern
<a href="#">Noridian Healthcare Solutions, LLC</a>	A and B MAC	01182 - MAC B	J - E	California - Southern American Samoa
<a href="#">Noridian Healthcare Solutions, LLC</a>	A and B MAC	01211 - MAC A	J - E	Guam Hawaii Northern Mariana Islands American Samoa
<a href="#">Noridian Healthcare Solutions, LLC</a>	A and B MAC	01212 - MAC B	J - E	Guam Hawaii Northern Mariana Islands
<a href="#">Noridian Healthcare Solutions, LLC</a>	A and B MAC	01311 - MAC A	J - E	Nevada
<a href="#">Noridian Healthcare Solutions, LLC</a>	A and B MAC	01312 - MAC B	J - E	Nevada American Samoa California - Entire State
<a href="#">Noridian Healthcare Solutions, LLC</a>	A and B MAC	01911 - MAC A	J - E	Guam Hawaii Nevada Northern Mariana Islands

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## LCD Information

### Document Information

LCD ID L37070	Original Effective Date For services performed on or after 09/22/2017
LCD Title MoIDX: DecisionDx-UM (Uveal Melanoma)	Revision Effective Date N/A
Proposed LCD in Comment Period N/A	Revision Ending Date N/A
Source Proposed LCD <a href="#">DL37070</a>	Retirement Date N/A
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	Notice Period End Date 09/21/2017

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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.

Title XVIII of the Social Security Act, §1833(e). Prohibits Medicare payment for any claim which lacks the necessary information to process the claim.

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

CMS On-Line Manual, Publication 100-02, Medicare Benefit Policy Manual, Chapter 15, §§80.0, 80.1.1, 80.2. Clinical Laboratory services.

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 Medicare contractor will provide limited coverage for the DecisionDx-UM (Castle Bioscience, Inc.) test for the management of newly diagnosed uveal melanoma. This test is intended for the determination of metastatic risk, and to guide surveillance and referral to medical oncology (preferably an oncologist with expertise in melanoma) in patients who have a confirmed diagnosis of uveal melanoma (UM) and no evidence of metastatic disease.

### **Summary of Evidence**

Uveal melanoma is a rare cancer, affecting ~1600-1700 patients per year in the United States, but it is the most common intra-ocular cancer in adults. Uveal melanoma arises in the middle layer of the eye, the uvea tract,

which consists of the iris, ciliary body, and choroid. Eye-sparing radiation (brachytherapy or proton beam therapy) is the most common treatment approach, but approximately 10% of patients will undergo enucleation due to large and/or aggressive tumors that cannot be managed with radiation or due to eye pain or vision loss. Local treatment by radiation or enucleation is highly successful at controlling the primary tumor, with only ~5% chance of local recurrence. Most patients present with local disease and no evidence of metastases, however, as many as 50% of patients will ultimately experience distant metastasis, most commonly to the liver.

Clinicopathologic staging cannot reliably identify patients at low or high risk of metastasis, as even early stage patients (AJCC Stage I-II) have a substantial risk of metastasis and mortality. Historically, most UM patients were managed with high intensity surveillance, including frequent imaging and laboratory tests, with the goal of diagnosing early metastasis. Systematic imaging has been shown to be effective at identifying asymptomatic metastases, which is important because treatment of liver metastases with surgical resection or regional therapy is more effective and achieves better outcomes when tumor burden is low. However, since approximately 50% of patients will not experience metastasis, a substantial proportion of patients were subjected to unnecessary imaging, laboratory tests, and clinical visits, resulting in patient burden, undue exposure to radiation and over-utilization of healthcare resources.

An accurate determination of metastatic risk at diagnosis allows for a risk-appropriate surveillance program. Patients at high-risk of metastasis can continue to be followed with a high intensity program as previously prescribed, such as quarterly ultrasound, MRI or CT scans alternating with LFTs, and consideration of adjuvant treatment. These patients benefit from early detection of metastatic disease when it can be most effectively treated. Patients with low metastatic risk can be removed from this traditional intensive surveillance and instead followed with a low intensity program, such as yearly exams, imaging, and liver function tests (LFTs).

### **DecisionDx-UM Test Description and Intended Use**

DecisionDx-UM is an RNA gene expression classifier that is based on the expression levels of 15 mRNA transcripts (3 control and 12 discriminating genes). DecisionDx-UM is performed on tissue from a fresh-frozen fine needle aspirate biopsy (FNAB), formalin-fixed paraffin embedded (FFPE) sections from an enucleated tumor, or, in rare cases, fresh-frozen resection material. Results are reported as a 5-year risk classification for metastasis: low risk (Class 1A), intermediate risk (Class 1B), or high risk (Class 2).

The DecisionDx-UM test is intended for determination of metastatic risk, and to guide surveillance and referral to medical oncology in patients who have a confirmed diagnosis of uveal melanoma (UM) and no evidence of metastatic disease. The test discriminates patients with high risk (class 2) for early distal recurrent disease from those with minimal risk of distal metastasis (class 1A). Identification of high-risk patients allows early referral to a medical oncologist with expertise in the management of uveal melanomas, which includes intensified metastatic surveillance and/or metastasis intervention, and stratification for entry into clinical trials with adjuvant therapy. In rare cases where the patient cannot realistically see a medical oncologist due to geographic location (long distance to travel), and/or are among underserved patient populations, if they cannot feasibly see a medical oncologist, surveillance testing for class 2 patients can be directed by an ophthalmologist with specific training in treating patients with uveal melanoma.

### **Clinical Validation**

In both prospective and retrospective multicenter studies, DecisionDX-UM has been shown to be a more accurate prognostic indicator of metastasis compared to any other factor.<sup>1-4</sup>

Onken et al. reported the migration of the RNA expression profile from a hybridization-based microarray platform to a PCR-based 15 gene assay and analyzed the technical performance of the assay in a prospective study of FNAB tumor samples from multiple centers. The gene expression profile distinguished between low metastatic risk (class 1 signature) and high metastatic risk (class 2 signature). The role of RNA quality and tumor heterogeneity was evaluated. A clinically annotated training set of 28 uveal melanomas was used to support the vector machine algorithm for classification. One hundred seventy-two (172) patients from a single center with a median follow-up of 16 months were utilized to evaluate prognostic performance which demonstrated technical performance of 94.8%. Kaplan–Meier analysis showed an accuracy of risk-classification with 5-year metastatic-free survival (MFS) rates of 98% and 24% for predicted Class 1 and 2 cases, respectively ( $P < 0.0001$ ).<sup>1</sup>

The Collaborative Ocular Oncology Group study was a prospective, multi-center, blinded study to assess clinical validity of the DecisionDx-UM test.<sup>2</sup> Comparison with other genetic and clinicopathologic variables was evaluated. Of 494 patients, 446 were considered evaluable. The 50-month metastasis-free survival was 97% vs 20% for Class 1 and 2 respectively ( $p < 0.0001$ ). By Cox multivariate proportional hazards analysis, Class 2 identified metastasis better than any other prognostic factor ( $p < 0.006$ ). The Net Reclassification Improvement study showed improvement of gene expression profiling over TNM (T describes size of primary tumor, N describes regional lymph nodes status, M describes distant metastasis) classification of 37% at 2 years ( $p = 0.008$ ) and 43% at 3 years ( $p = 0.001$ ). When compared to chromosome 3 status, the improvement of gene expression profiling

over TNM was 36% at 2 years (p= 0.006) and 38% at 3 years (p=0.004).<sup>2</sup>

In a retrospective, single-center clinical study designed to assess clinical validity of the DecisionDx-UM test, in 187 patients, Chappell, et al. showed disease specific survival was predicted with high accuracy.<sup>3</sup> Kaplan-Meier analysis for 5-year disease specific survival was 93% and 38% for Class 1 vs 2 cases, respectively (p<0.0001). By multivariate Cox modeling, the DecisionDx-UM class was the only independent significant predictor of outcome for both metastasis-free survival (HR=8.4, p<0.0001) and disease-specific survival (HR=12.3, p<0.0001).

Another prospective, single-center clinical study evaluated the clinical validity of the DecisionDx-UM test in 299 UM patients. In this study, Cox multivariate analyses confirmed that the 15-gene expression profile was the only significant predictor of metastatic risk (p=0.0013).<sup>4</sup>

A step-down algorithm analysis of two genes in Class 1 patients has since been performed to identify those patients with Class I classification at risk for late metastasis. Due to this refinement, Class 1 includes low-risk Class 1A patients and a small number of intermediate-risk Class 1B subjects with late relapse.

## Clinical Utility

A retrospective chart review study showed that the DecisionDx-UM test results direct appropriate surveillance and treatment plans by matching an individual patient's risk for metastasis to informed medical management decisions. Aaberg et al. reported on 88 Medicare beneficiaries in which all Class 1 patients received low-intensity surveillance while Class 2 patients received high intensity surveillance plans (imaging and/or liver function testing every 3-6 months). Test results also influenced referral decisions with 29% of Class 2 patients being referred to medical oncology for follow-up and 10% recommended for adjuvant therapy consideration whereas no Class 1 patients were referred.

In a prospective, multi-center study of 70 patients, the majority (81%) of Class 1 patients had low-intensity surveillance and all (100%) Class 2 patients received high-intensity surveillance (p<0.0001); four Class 2 patients were recommended for systemic adjuvant therapy.

A decision tree analysis was performed to model the impact of DecisionDx-UM on resource utilization, comparing the previous framework in which all patients received high-intensity surveillance regimens with one in which the surveillance regimen is guided by DecisionDx-UM. Strict compliance with DecisionDx-UM results was associated with a 50% reduction in the number of surveillance procedures performed at two years compared to the previous framework, and a 63% reduction at five years. These results indicate that use of DecisionDx-UM can help avoid high intensity, imaging-based surveillance in patients with a low risk of metastasis, thereby reducing resource utilization in the management of uveal melanoma patients, which is associated with overall cost savings.

## Summary of Analytical and Clinical Performance

### General

Intended Use	The DecisionDx-UM test is intended for the determination of metastatic risk, and to guide surveillance and referral to medical oncology in patients who have a confirmed diagnosis of uveal melanoma (UM) and no evidence of metastatic disease.
Validated Specimen Type(s)	Fresh frozen fine needle aspirate biopsies (FNAB), frozen resections, and formalin-fixed, paraffin-embedded (FFPE) specimens

### Analytical Performance

Description	Results (with 95% Confidence Intervals if applicable) <sup>1</sup>
Repeatability (within run precision) 4 samples (in triplicate) twice on a single PCR card, 1 instrument, 1 operator, 1 run, 1 day, 1 manufacturing reagent lot; repeated on a separate card.	100% (63.1-100%)
Intermediate precision (between run precision)	89.3% (71.8-97.7%) 100% (79.4-100%)

**Inter-operator/instrument:**

28 samples, 2 instruments, 2 operators, 2 runs, 1 day, 1 manufacturing reagent lot (3 discordances: 1 class 2 vs 1A; 2 class 1A-1B)

**Inter-assay:** 16 samples, 1 instrument, 2 operators, 3 runs, 3 consecutive days, 1 manufacturing lot (0 discordances)

Reproducibility (between sites)	Not applicable
Minimum input cDNA quantity	125 ng
Minimum tumor content (for FFPE specimens)	80% by histomorphology
Limit of blank (LOB)	CT undetermined for blank
Limit of detection (LOD)	Not applicable
Limit of quantitation (LOQ)	Not applicable
Linearity	Not applicable
Interfering substances	Not applicable <sup>2</sup>
Specimen stability, primary	FNAB 96 hours at -80 °C (Onken et al., 2010) FFPE 4 years at RT (Onken et al., 2012)
Specimen stability, intermediate (extracted RNA)	96 hours when stored at -80 °C per manufacturer and literature
Specimen stability, intermediate (cDNA)	24 hours when stored at 4 °C per manufacturer 30 days when stored at -20 °C Applied Biosystems TaqMan® Low Density Array, 24 months at -20 °C per manufacturer  Arcturus PicoPure® RNA Extraction Kit, 10 months at RT per manufacturer  Applied Biosystems High-Capacity cDNA Reverse Transcription Kit, 8 months at -20 °C per manufacturer
Critical reagent closed/shelf-life stability	Applied Biosystems TaqMan® PreAmp Master Mix Kit, 9 months at 4 °C per manufacturer  Applied Biosystems TaqMan® Gene Expression Master Mix, 12 months at -20 °C per manufacturer  Applied Biosystems RNase Inhibitor, 42 months at -20 °C per manufacturer
Critical reagent open/in use stability	Per manufacturer's specifications

<sup>1</sup>Using Clopper-Pearson method

<sup>2</sup>Since the gene expression profile is based on ratios of gene to controls, rather than an absolute value, the effect

of an interfering agent is expected to affect all genes equally and result in failed amplification.

## Clinical Performance: Validity

Description	5-year metastasis-free or disease-specific survival rates <sup>1</sup> (Non-censored recurrence rate; 95% Confidence Intervals of event rates) <sup>2</sup>		
	Class 1A	Class 1B	Class 2
Onken et al., 2012 <sup>2</sup> (n=514)*	98% <sup>a</sup> (0.8%; 0.1-3%; 2/241)	79% <sup>a</sup> (10.4%; 4.3-20.3%; 7/67)	28% <sup>a</sup> (29.6%; 23.5-36.4%; 61/206)
Chappell et al., 2012 <sup>3</sup> (n=187)*	93% <sup>b</sup> (2.5%; 0.5-7.3%; 3/118)		38% <sup>b</sup> (28.9%; 18.7-41.2%; 20/69)
Correa et al., 2014 <sup>4</sup> (n = 158) <sup>†</sup>	92% <sup>b</sup> (4.58%; 1.5-10.4%; 5/109)		55% <sup>b</sup>
Demirci, et al. 2015 <sup>5</sup> (n = 203) <sup>†**</sup>	95% <sup>a</sup>	90% <sup>a</sup>	27% <sup>a</sup>
Correa et al., 2016 <sup>6</sup> (n = 299) <sup>†</sup>	92% <sup>b</sup>		55% <sup>b</sup>

<sup>1</sup>Survival rates according to Kaplan-Meier analysis

<sup>2</sup>Overall non-censored recurrence rates and 95% Confidence Intervals (Coppler-Pearson method) not accounting for censored patients.

\*Tests performed at Washington University (Wash U);

†Tests performed at Wash U and Castle Biosciences Inc.

\*\*Published survival rates but not event numbers so cannot calculate confidence intervals

## Clinical Performance: Utility

Description	Clinical Use Outcomes (with 95% Confidence Intervals if applicable) <sup>1</sup>		
	Class 1A	Class 1B	Class 2
Aaberg et al., 2014 <sup>7</sup> (n = 88 with documentation)			100.0%

(Note: Retrospective decision impact study of Medicare beneficiaries)	100% (92.6-100.0%; 48/48) received low intensity surveillance. None referred to medical oncology or adjuvant trials. <sup>1</sup>	(91.2-100.0%; 40/40) received high intensity surveillance, referral to medical oncology or adjuvant trials.
Plasseraud et al., 2016 <sup>8</sup> (n = 70)	(65.3-94.4%; 25/30) received low intensity management 16.7% (5.6-34.7%; 5/30) received high intensity management 10.0% (2.1-26.5%; 3/30) received referral to medical oncology	(29-96.3%; 5/7) received low intensity management 28.6% (3.7-71.0%; 2/7) received high intensity management 33.3% (18.0-51.8%; 11/33) received referral to medical oncology

<sup>1</sup>Low intensity management is defined liver function tests (LFTs) and/or imaging studies annually. High intensity management is defined liver function tests and/or imaging studies every 3-6 months.

**Analysis of Evidence  
(Rationale for Determination)**

*Level of Evidence*

Quality – Moderate

Strength – Limited

Weight – Limited

This contractor recognizes that evidence for clinical utility for the DecisionDX-UM assay in patients with uveal melanoma with no evidence of distant metastatic disease at the time of diagnosis is promising at the current time. However, this contractor believes a prospective registry currently in progress will generate sufficient data to demonstrate improved patient outcomes. Registry endpoints will demonstrate that ≥ 80% of class 2 patients are referred to medical oncology for management, and that Class 1A/1B patients do not undergo more intensive surveillance testing compared to Class 2 patients. Continued coverage of this assay will depend on semi-annual review of interim data and publications demonstrating the above clinical utility.

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# 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:

81599 UNLISTED MULTIANALYTE ASSAY WITH ALGORITHMIC ANALYSIS

## ICD-10 Codes that Support Medical Necessity

**Group 1 Paragraph:** N/A

### Group 1 Codes:

#### ICD-10 Codes

#### Description

C69.31	Malignant neoplasm of right choroid
C69.32	Malignant neoplasm of left choroid
C69.41	Malignant neoplasm of right ciliary body
C69.42	Malignant neoplasm of left ciliary body
C69.91	Malignant neoplasm of unspecified site of right eye
C69.92	Malignant neoplasm of unspecified site of left eye

ICD-10 Codes that DO NOT Support Medical Necessity N/A

ICD-10 Additional Information [Back to Top](#)

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# General Information

## Associated Information

N/A

## Sources of Information

N/A

### Bibliography

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5. Demirci, et al. (2015). Gene expression profiling test of uveal melanoma: prognostic validation, in American Society of Ophthalmic Plastic & Reconstructive Surgery Fall Scientific Symposium: Las Vegas, NV.
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7. Aaberg, T.M., Jr., et al., Current clinical practice: differential management of uveal melanoma in the era of molecular tumor analyses. Clin Ophthalmol, 2014. 8: p. 2449-60.
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## **Revision History Information**

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## **Associated Documents**

Attachments N/A

Related Local Coverage Documents Article(s) [A55657 - Response to Comments: MoIDX DecisionDX Uveal Melanoma](#) LCD(s) [DL37070 - MoIDX: DecisionDx-UM \(Uveal Melanoma\)](#)

Related National Coverage Documents N/A

Public Version(s) Updated on 07/20/2017 with effective dates 09/22/2017 - N/A [Back to Top](#)

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## **Keywords**

- Decision DX-UM
- Uveal
- Melanoma
- 81599
- MoIDX
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