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

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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

LCD ID **Original Effective Date**

L37070

LCD Title
MolDX: DecisionDx-UM (Uveal Melanoma)

Proposed LCD in Comment Period
N/A

Source Proposed LCD
DL37070

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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.

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.

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, undo 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.[1-4]

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 ($P < 0.0001$).[1]

The Collaborative Ocular Oncology Group study was a prospective, multi-center, blinded study to assess clinical validity of the DecisionDx-UM test.[2] 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 ($p=0.004$).[2]

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.[3] 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).[4]

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)[1]
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) **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)	89.3% (71.8-97.7%) 100% (79.4-100%)
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[2]
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 7deg;C per manufacturer
Critical reagent closed/shelf-life stability	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 Applied Biosystems TaqMan® PreAmp Master Mix Kit, 9 months at 4 7deg; 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

[1]Using Clopper-Pearson method

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

[1]Survival rates according to Kaplan-Meier analysis

[2]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)[1]**		
	Class 1A	**Class 1B**	**Class 2**
Aaberg et al., 2014[6] (n = 88 with documentation) (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.[1]		100.0% (91.2-100.0%; 40/40) received high intensity surveillance, referral to medical oncology or adjuvant trials.
Plasseraud et al., 2016[7] (n = 70)	(65.3-94.4%; 25/30) received low intensity management 16.7% (5.6-34.7%; 5/30)	(29-96.3%; 5/7) received low intensity management 28.6% (3.7-71.0%; 2/7) received	(89.4-100.0%; 33/33) received high intensity management

received high intensity management	high intensity management	
10.0% (2.1-26.5%; 3/30) received referral to medical oncology		33.3% (18.0-51.8%; 11/33) received referral to medical oncology

[1]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.

General Information

Associated Information

N/A

Sources of Information

N/A

Bibliography

1. Onken MD, et al. An accurate, clinically feasible multi-gene expression assay for predicting metastasis in uveal melanoma. J Mol Diagn. 2010;12(4):461-8.

2. Onken MD, et al. Collaborative Ocular Oncology Group report number 1: prospective validation of a multi-gene prognostic assay in uveal melanoma. Ophthalmology, 2012;119(8):1596-603.

3. Chappell MC, et al. Uveal melanoma: molecular pattern, clinical features, and radiation response. Am J Ophthalmol, 2012;154(2):227-32 e2.

4. Correa & Augsburger. (2014). Sufficiency of FNAB aspirates of posterior uveal melanoma for cytologic versus GEP classification in 159 patients, and relative prognostic significance of these classifications. Graefe's Archive for Clinical and Experimental Ophthalmology, 252(1), 131-5.

5. Correa ZM and Augsburger JJ. Independent prognostic significance of gen expression profile class and largest basal diameter of posterior uveal melanomas. Am J Ophthalmol. 2016;162:20-7 e1.

6. 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.

7. Plasseraud, K.M., et al., Clinical Performance and Management Outcomes with the DecisionDx-UM Gene Expression Profile Test in a Prospective Multicenter Study. Journal of Oncology, 2016. 2016: p. 1-9.m J Ophthalmol. 2016;162:20-7 e1.

Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
12/01/2019	R4	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, to remove all coding from LCDs. 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: DecisionDx-UM (Uveal Melanoma) A57621 Article. *At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires*	• Provider Education/Guidance

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
		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.	
12/01/2019	R3	As required by CR 10901, all billing and coding information has been moved to the companion article, this article is linked to the LCD. 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.	• Revisions Due To Code Removal
02/21/2019	R2	R1 stated the removal of the Demirci reference in the Clinical Performance Validity Table and in the Bibliography section. It was not removed from the table and this revision removes it.	• Creation of Uniform LCDs With Other MAC Jurisdiction • Typographical Error
02/21/2019	R1	Added 0081U to CPT/HCPCS Codes Group 1. The change is due to the Q1:2019 CPT/HCPCS Quarterly Update and is effective 1/1/2019. Deleted 81599. Deleted the Demirci reference in the Clinical Performance Validity Table and in the Bibliography section.	• Revisions Due To CPT/HCPCS Code Changes

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Article(s)
A57621 - Billing and Coding: MolDX: DecisionDx-UM (Uveal Melanoma)
A55657 - Response to Comments: MolDX DecisionDX Uveal Melanoma
LCD(s)
DL37070
- (MCD Archive Site)

Related National Coverage Documents

N/A

Public Version(s)

Updated on 12/13/2019 with effective dates 12/01/2019 - N/A
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Updated on 03/28/2019 with effective dates 02/21/2019 - 11/30/2019
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Updated on 07/20/2017 with effective dates 09/22/2017 - N/A

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