Local Coverage Determination (LCD): MolDX: DecisionDx-Melanoma (L37748)

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Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATE(S)
Noridian Healthcare Solutions, LLC	A and B MAC	02101 - MAC A	J - F	Alaska
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
Noridian Healthcare Solutions, LLC	A and B MAC	02302 - MAC B	J - F	Oregon
Noridian Healthcare Solutions, LLC	A and B MAC	02401 - MAC A	J - F	Washington
Noridian Healthcare Solutions, LLC	A and B MAC	02402 - MAC B	J - F	Washington
Noridian Healthcare Solutions, LLC	A and B MAC	03101 - MAC A	J - F	Arizona
Noridian Healthcare Solutions, LLC	A and B MAC	03102 - MAC B	J - F	Arizona
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Noridian Healthcare Solutions, LLC	A and B MAC	03301 - MAC A	J - F	North Dakota
Noridian Healthcare Solutions, LLC	A and B MAC	03302 - MAC B	J - F	North Dakota
Noridian Healthcare Solutions, LLC	A and B MAC	03401 - MAC A	J - F	South Dakota
Noridian Healthcare Solutions, LLC	A and B MAC	03402 - MAC B	J - F	South Dakota
Noridian Healthcare Solutions, LLC	A and B MAC	03501 - MAC A	J - F	Utah
Noridian Healthcare Solutions, LLC	A and B MAC	03502 - MAC B	J - F	Utah
Noridian Healthcare Solutions, LLC	A and B MAC	03601 - MAC A	J - F	Wyoming
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LCD Information

Document Information

LCD ID **Original Effective Date**

L37748

For services performed on or after 02/10/2019

LCD Title
MolDX: DecisionDx-Melanoma

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N/A

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Notice Period Start Date
12/26/2018

Notice Period End Date
02/09/2019

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

The DecisionDx-Melanoma test is covered only when the following clinical conditions are met:

- Patients diagnosed with clinical stage, sentinel lymph node biopsy (SLNB) eligible, T1 and T2 cutaneous melanoma tumors (as defined in AJCC Staging Manual v8, 2017) with clinically negative sentinel node basins who are being considered for SLNB to determine eligibility for adjuvant therapy. (Per current NCCN and ASCO guidelines, SLNB eligible patients are defined as:
    - Patients with T1a tumors:
        - in whom there is significant uncertainty about the adequacy of microstaging (positive deep margin), or
        - with Breslow depth <0.8 mm and with other adverse features (e.g. very high mitotic index [≥2/mm2], lymphovascular invasion, or a combination of these factors)
    - Patients with T1b tumors (≥0.8 mm or < 0.8 mm with ulceration)
- Patients with T2 tumors

Claims for DecisionDx-Melanoma testing will be denied when testing does not meet all of the above criteria.

Summary of Evidence

Background

Cutaneous melanoma (CM) is increasing in incidence in the U.S., with more than 87,000 cases expected to be diagnosed in 2017 and nearly 10,000 deaths each year [1]. Of these, more than 70,000 patients are diagnosed with Stage I or II disease (localized) as determined by the American Joint Committee on Cancer (AJCC) staging system [1]. Patients with early stage melanoma (i.e. AJCC Stage I-II) are regarded as good-prognosis based on population-based risk estimates. However, due to the greater number of individuals

within these earlier stages, more than twice as many people diagnosed with early stage disease will ultimately die of melanoma compared to those diagnosed with Stage III melanoma [2].

The DecisionDx-Melanoma test is a 31-gene expression profile (GEP) that determines a CM patient's risk for metastatic disease [3-6]. The test classifies patients as having a tumor with low (Class 1) or high (Class 2) risk for developing metastasis within 5 years of diagnosis. Patients with a Class 1 tumor profile also have a low likelihood of being sentinel lymph node (SLN) positive. Thus, the individualized risk profile result of this test can be used to guide use of SLNB in the context of patient-specific management plans.

Per current national guidelines, a SLNB procedure is considered for all patients with melanoma pathologic Stage T1b and above, as well as those patients with T1a tumors in whom there is significant uncertainty about the adequacy of microstaging [7, 8]. Patients with a positive SLN are at substantially increased risk for distant metastatic disease and death [2], however, the procedure only provides prognostic information, and the MSLT-II study showed no survival benefit associated with completion lymphadenectomy in SLN positive patients [9]. Currently, the identification of SLN positive patients helps identify Stage III patients who can potentially benefit from targeted and immunotherapeutic agents in the adjuvant setting [10-13]. The procedure can be associated with complications in a substantial proportion of patients such as pain, seromas, nerve damage and edema, and requires a large team of dedicated personnel, including nuclear medicine physicians, surgeons, and pathologists [14-16]. It has been estimated that the cost of a SLNB can be 10 times that of a wide excision alone, and the cost per life saved in a patient population with low prevalence of positive SLN can approach 1 million dollars [17]. Overall, the likelihood of a positive SLN after the SLNB procedure is 16% [2, 18], but this is variable for specific populations [18-21]. Elderly patients account for a substantial proportion of CM patients, and 60% of melanoma-related deaths occur in patients ≥65 years-old. While older age is associated with a poor prognosis, fewer elderly patients are SLN positive [19-23], which indicates that the prognostic value of SLNB is limited in this population [24, 25].

In general, a 5% likelihood for a positive SLN is recommended as a threshold for performing this procedure in a patient population [18]. Analysis of Castle's retrospective cohort (n=782) identified that DecisionDx-Melanoma Class 1A patients (probability score <0.5) with tumors who had a Breslow thickness (BT) of ≤2.0 mm (AJCC T1-T2) achieved a positive SLNB rate below 5% [26]. To validate this clinical use of the Class 1A cut-point for the DecisionDx-Melanoma test, two contemporary, multi-center, prospective study cohorts were tested: 584 patient cohort from two published prospective studies (overall 14% SLN positive rate) [6, 27] and a 837 patient cohort from prospectively tested patients at 5 large academic institutions (overall 12% SLN positive rate) [26]. The rate of SLN positivity in both prospective study cohorts aligns with the SLN positivity rate in the general population of melanoma patients who have undergone SLNB. The results show that in patients from the Medicare-eligible population (65 years old and over) who had a SLNB performed, those patients who had a DecisionDx-Melanoma Class 1A T1 or T2 tumor, have a 98.4% probability of being SLN negative. Thus, in this patient group, the DecisionDx-Melanoma test achieves a NPV that is comparable to other molecular tests used to guide surgical management decisions [28-31].

Analysis of the two prospective cohorts combined (n=1,421 patients) shows that SLN positivity rates are enriched from 12.8% using current SLNB criteria to 18.6% in those patients who would undergo the SLN biopsy procedure (T1/T2 with a Class 2 DecisionDx-Melanoma test result and T3/T4 patients). The rate of SLN positivity in the 65 years and older population from Castle's prospective cohort (n=629) is 14.6% of Class 1A patients and 11.9% for Class 2B patients. SLNB positivity rates for T3 tumors is 8.7% for Class 1A compared to 18% for Class 1B-2B; for T4 tumors it is 17% and 17% respectively. Importantly, the 5-year melanoma specific survival (MSS) rate for T1/T2 Class 1 patients remains favorable; with 99% MSS, comparable to that observed in T1a tumors and for which current guidelines do not recommend SLNB [7, 32, 33]. Furthermore, T1/T2 Class 1 patients show 5-year overall survival (OS) of 97% and distant metastasis free survival (DMFS) of 93% [33]. The MSLT-II study demonstrated that a delay in lymph node dissection does not adversely affect survival, thus clinical follow up of Class 1 patients and lymphadenectomy for those few who develop clinically detectable nodal disease should achieve similar outcomes to those who currently undergo a planned SLNB [9]. Thus, the test identifies a patient population with <5% likelihood of a positive SLN and high survival rates and therefore has utility in guiding SLNB decisions in patients 65 years-old and over with T1-T2 CM tumors. In this population, the test could potentially reduce the rate of SLNB by up to 78%

while still maintaining a MSS survival rate of 99% in those patients with low-risk tumor biology who can safely avoid the procedure.

Clinical validation of DecisionDx-Melanoma as a prognostic test for CM patients was performed in three multicenter, prospectively designed archival tissue studies including 782 patients [3-5]. These studies have shown that the test accurately predicts risk for local/regional recurrence, distant metastasis, melanoma-related mortality, and all-cause mortality independent of clinicopathologic factors used in staging and that the test shows improved sensitivity and negative predictive value (NPV) for recurrence-free (RFS), distant metastasis-free (DMFS), melanoma-specific (MSS) and overall (OS) survival individually or in conjunction with established clinicopathologic factors. Three prospective, independent studies (n= 510) and an interim analysis of two prospective registries (n=322) have confirmed the prognostic accuracy of DecisionDx-Melanoma [6, 34-36].

The DecisionDx-Melanoma test may improve net health outcomes by accurately identifying patients who are at risk of developing metastatic disease and would otherwise go undetected, as well as patients with a low likelihood of having a positive SLN. Net health outcomes are improved for low risk Class 1 patients who can consider avoiding SLNB and associated surgical and anesthesia risk (T1-T2 patients), as well as intensive follow up and exposure to radiation from imaging procedures, and for high risk Class 2 patients by improved guidance to perform SLNB.

Summary of Analytical and Clinical Performance

General

Intended Use	The DecisionDx-Melanoma test is intended for SLNB-eligible T1 and T2 cutaneous melan (as defined in AJCC Staging Manual v8, 2017) with clinically negative sentinel node basi being considered for SLNB to determine eligibility for adjuvant therapy
Validated Specimen Type(s)	Formalin-fixed, paraffin-embedded (FFPE) specimens of the primary tumor.

Analytical Performance [37]

Description	Results (with 95% Confidence Intervals if applicable)[1]
Repeatability (within run precision) 21 samples (in triplicate) three PCR cards, 1 instrument, 1 operator, 3 runs 2 days, 1 manufacturing reagent lot.	Binary Classification (Class 1 / Class 2): 100% (94-100%) Subcla (Class 1A/1B; Class 2A/2B): 98% (91-100%)
Intermediate precision (between run precision)	
Inter-operator/instrument: 22 samples, 2 instruments, 2 operators, 2 runs, 2 day, 1 manufacturing reagent lots	Binary Classification (Class 1 / Class 2): 95% (77-100.0%) Subcla (Class 1A/1B; Class 2A/2B): 95% (77-100%)
Inter-assay: 143 samples, 2 instruments, 2 operators, 15 runs, multiple days (2.5 year interval), multiple manufacturing lots	Binary Classification (Class 1 / Class 2): 99% (96-100.0%) Subcla (Class 1A/1B; Class 2A/2B): 92% (87-96%)
Reproducibility (between sites)	Not applicable
Minimum input RNA quantity	5 ng RNA
Minimum tumor content (for FFPE specimens)	40% by histomorphology
Limit of blank (LOB)	CT undetermined for blank
Limit of detection (LOD)	Not applicable
Limits of quantitation (LOQ)	Not applicable
Linearity	Not applicable

Interfering substances	Not applicable[2]
Specimen stability, primary	FFPE x 4 years at RT per literature and up to 16 years in outcor analysis from validation cohort
Specimen stability, intermediate (extracted RNA)	96 hours when stored at -80°C per SOP
Specimen stability, intermediate (cDNA)	96 hours when stored at 4°C per SOP 30 days when stored at -20
Critical reagent closed/shelf-life stability (manufacturer's recommendations/lab validated)	Applied Biosystems TaqMan® Low Density Array, -20°C x 24 mont months (lab) Applied Biosystems TaqMan® Open Array, -20°C x 1 3 months (lab) Applied Biosystems High-Capacity cDNA Reverse Tr Kit , -20 °C x 8 months / 3 months (lab) Applied Biosystems TaqMan® PreAmp Master Mix Kit, 4°C x 9 mon months (lab) Applied Biosystems TaqMan® OpenArray Master Mix, -20°C x 12 m months (lab) Applied Biosystems RNAse Inhibitor, -20 °C x 42 months / 3 month Qiagen Deparaffinization Solution, room temperature x 3 months Q Buffer PKD, room temperature x 3 months Qiagen Dnase Booster Buffer, room temperature x 3 months Qiage K, room temperature x 3 months Qiagen QIAsymphony RNA kit, room temperature x 3 months
Critical reagent open/in use stability	Per lab validation or 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: Utility

Data below shows that using the DecisionDx-Melanoma test for SLNB guidance in T1/T2 as defined by AJCC v8 identifies a patient population with <5% likelihood of a positive SLN with high rates of MSS, OS and DMFS, OS and therefore may have utility in guiding SLNB decisions in Medicare patients. In this population, the test will reduce the rate of SLNB by up to 52% while still maintaining a MSS survival rate of 99% in those patients with low-risk tumor biology who can safely avoid the procedure.

Summary of DecisionDx-Melanoma performance in SLNB guidance in T1/T2 melanoma patients ≥65 years old, eligible for SLNB biopsy

Cohort	Overall N	NPV	SLN+ Rate T1/T2 Patients	SLN+ Rate T1/T2 Class 1B-2B Patients	SLN+ Rate All Patients Directed to SLN
Castle Prospective Studies[c]	193	0.99 (0.93-1)	3.33%	7.32%	15.79%
Independent Validation Cohort[d]	335	0.97 (0.93-0.99)	5.29%	10.00%	12.23%
Combined	528	0.98 (0.95-0.99)	4.61%	9.09%	13.58%

NPV = Negative Predictive Value in for SLN positivity in SLNB eligible T1/T2 patients with Class 1A DecisionDx-Melanoma test result

[a]Patients eligible for SLNB per NCCN guidelines or had a SLNB procedure performed

[b]SLNB positive rate in all patients undergoing SLNB after guidance with test (T1/T2 Class 1B-2B and T3/T4)

[c]Data from two contemporary, prospective, multicenter studies (total n=584) [6, 27]
[d]Data from independent cohort from 5 academic centers (total n=837) [26]

Expected survival outcomes in T1/T2 patients who avoid or undergo SLNB based on DecisionDx-Melanoma class result

Patient Group	MSS	OS	DMFS
T1/T2 Class 1 (No SLNB)	99.3%	97.2%	93.4%
T1/T2 Class 2 SLNB Negative	95.3%	95.3%	86.3%
T1/T2 Class 2 SLNB Positive	73.8%	52.4%	52.5%

Data from three retrospective, multicenter cohorts (N=690)
Median follow up time of cohort = 6.5 yr [3-5, 26]
Note: Limited data for Class 1 T1/T2 patients who were found to be SLNB positive under current guidelines showed MSS, OS and DMFS rates of 100%, 90.7 and 75.7%.

Clinical Performance: Validity

Summary of event rates in DecisionDx-Melanoma clinical validity studies

			Non-censored recurrence rate (95% CI) Events/Total Class		Non-censo (95%
Study	Design	Population	Class 1	Class 2	Class
Gerami et al., 2015 CCRa [3]	Archival, prospective design	Stage I-II, n=78; mf/u: 5.7 years	5.8% (1.2-16%) 3/52	69% (48-86%) 18/26	3.8% (0.47 2/52
Gerami et al., 2015 JAADb [4]	Archival, prospective design	SLN-eligible, Stage I-III, n=217; mf/u: 4.2 years	21% (13-32%) 16/76	65% (56-72%) 91/141	18% (10- 14/7
Zager et al., 2017 [5]	Archival, prospective design	Stage I-III, n=523; mf/u: 6.1 years	13% (9.8-18%) 42/314	48% (41-55%) 100/209	9% (6-1 28/31
Greenhaw et al., 2017 [34]	Consecutively tested, single center	Stage I-II, n=256; mean f/u: 1.9 years	1.4% (0.3-4%) 3/214	24% (12-39%) 10/42	
Hsueh et al., 2017 [35]	Prospective, single center	Stage I-III, n=159; mf/u: 2.1 years	2.6% (0.53-7.3%) 3/117	45% (30-61%) 19/42	
Hsueh et al., 2017 [6]	Prospective registries	Stage I-III, n=322; mf/u: 1.5 years	2% (0.66-4.6%) 5/248	27% (17-38%) 20/74	1% (0.1-2 2/24
Renzetti et al., 2017 [36]	Consecutively tested, single center	Stage I-III, n=95; mf/u: 0.9 years	4.9% (0.6-17%) 2/41	24.1% (13-38%) 13/54	2.4% (0.06- 1/41

mf/u = median follow-up
Confidence intervals calculated by the Coppler-Pearson method
[a]Recurrence in Gerami et al., 2015 CCR included sentinel lymph node positivity as an event, while all other studies did not. Therefore, for this study, only Stage I-II patients are included.
bPatients in this study were eligible for SLNB so they include Stage I-II patients at a higher risk of metastasis, thus event rates in Class 1 is expected to be higher than in other studies.

Summary of survival outcomes in DecisionDX-Melanoma clinical validity studies

			Recurrence-free Survival (RFS) rate (95% CI)	
Study	Design	Population	Class 1	Class 2

Gerami et al., 2015 CCRa [3]	Archival, prospective design	Stage I-II, n=78; mf/u: 5.7 years	98% (93-100%)[c]	37% (21-56%)
Gerami et al., 2015 JAADb[4]	Archival, prospective design	SLN-eligible, Stage I-III, n=217; mf/u: 4.2 years	79% (70-90%)[c]	33% (26-43%)
Zager et al., 2017 [5]	Archival, prospective design	Stage I-III, n=523 mf/u: 6.1 years	88% (85-92%)[c]	52% (46-60%)
Greenhaw et al., 2017 [34]	Consecutively tested, single center	Stage I-II, n=256; mean f/u: 1.9 years	98% (95-100%)[d]	74% (59-93%)
Hsueh et al., 2017 [35]	Prospective, single center	Stage I-III, n=159 mf/u: 2.1 years	97% (95-100%)[e]	54% (41-72%)
Hsueh et al., 2017 [6]	Prospective registries	Stage I-III, n=322 mf/u: 1.5 years	97% (95-100%)[f]	77% (67-88%)

mf/u = median follow-up
Survival rates and confidence intervals calculated by Kaplan-Meier method
[a]Recurrence in Gerami et al., 2015 CCR included sentinel lymph node positivity as an event, while all other studies did not. Therefore, for this study, only Stage I-II patients are included.
[b]Patients in this study were eligible for SLNB so they include Stage I-II patients at a higher risk of metastasis, thus event rates in Class 1 is expected to be higher than in other studies
[c]5-year survival outcomes
[d]3-year survival outcomes
[e]2-year survival outcomes
[f]1.5-year survival outcomes

Analysis of Evidence
(Rationale for Determination)

Level of Evidence

Quality of evidence – Moderate
Strength of evidence – Low
Weight of evidence - Low

This contractor will cover the DecisionDx-Melanoma test for patients diagnosed with SLNB eligible T1b and T2 tumor who are being considered for SLNB. The DecisionDx-Melanoma assay should not be ordered if a patient and his/her physician do not intend to act upon the test result. Continued coverage is dependent on the publication and/or presentation of additional clinical utility data demonstrating the impact of the test's use on patient management decisions with (1) 95% or greater DMFS and MSS at 3 years in patients directed to no SLNB by the test compared to standard of care, and (2) evidence of higher SLNB positivity in patients selected for this procedure by the test compared to standard of care.

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
81599	UNLISTED MULTIANALYTE ASSAY WITH ALGORITHMIC ANALYSIS

ICD-10 Codes that Support Medical Necessity

Group 1 Paragraph:

N/A

Group 1 Codes:

ICD-10 CODE	DESCRIPTION
C43.0	Malignant melanoma of lip
C43.10	Malignant melanoma of unspecified eyelid, including canthus
C43.111	Malignant melanoma of right upper eyelid, including canthus
C43.112	Malignant melanoma of right lower eyelid, including canthus
C43.121	Malignant melanoma of left upper eyelid, including canthus
C43.122	Malignant melanoma of left lower eyelid, including canthus

ICD-10 CODE	DESCRIPTION
C43.20	Malignant melanoma of unspecified ear and external auricular canal
C43.21	Malignant melanoma of right ear and external auricular canal
C43.22	Malignant melanoma of left ear and external auricular canal
C43.30	Malignant melanoma of unspecified part of face
C43.31	Malignant melanoma of nose
C43.39	Malignant melanoma of other parts of face
C43.4	Malignant melanoma of scalp and neck
C43.51	Malignant melanoma of anal skin
C43.52	Malignant melanoma of skin of breast
C43.59	Malignant melanoma of other part of trunk
C43.60	Malignant melanoma of unspecified upper limb, including shoulder
C43.61	Malignant melanoma of right upper limb, including shoulder
C43.62	Malignant melanoma of left upper limb, including shoulder
C43.70	Malignant melanoma of unspecified lower limb, including hip
C43.71	Malignant melanoma of right lower limb, including hip
C43.72	Malignant melanoma of left lower limb, including hip
C43.8	Malignant melanoma of overlapping sites of skin
C43.9	Malignant melanoma of skin, unspecified
D03.111	Melanoma in situ of right upper eyelid, including canthus
D03.112	Melanoma in situ of right lower eyelid, including canthus
D03.121	Melanoma in situ of left upper eyelid, including canthus
D03.122	Melanoma in situ of left lower eyelid, including canthus

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

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Revision History Information

N/A

Associated Documents

Attachments

N/A

Related Local Coverage Documents

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