# Local Coverage Determination (LCD):
# MolDX: Melanoma Risk Stratification Molecular Testing (L37750)

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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<br>Guam<br>Hawaii<br>Northern Mariana Islands |
| Noridian Healthcare Solutions, LLC | A and B MAC | 01212 - MAC B | J - E | American Samoa<br>Guam<br>Hawaii<br>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<br>California - Entire State<br>Guam<br>Hawaii<br>Nevada<br>Northern Mariana Islands |

# LCD Information

## Document Information

**LCD ID** **Original Effective Date**

L37750

**LCD Title**
MolDX: Melanoma Risk Stratification Molecular Testing

**Proposed LCD in Comment Period**
N/A

**Source Proposed LCD**
DL37750

**AMA CPT / ADA CDT / AHA NUBC Copyright Statement**


For services performed on or after 02/10/2019

**Revision Effective Date**
For services performed on or after 12/06/2020

**Revision Ending Date**
N/A

**Retirement Date**
N/A

**Notice Period Start Date**
10/22/2020

**Notice Period End Date**
12/05/2020

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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 Internet-Only Manuals, Publication 100-04, Medicare Claims Processing Manual, Chapter 16, §50.5 Jurisdiction of Laboratory Claims, 60.12 Independent Laboratory Specimen Drawing, 60.1.2. Travel Allowance.

## Coverage Guidance

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

Molecular diagnostic tests used to assist in risk stratification of melanoma patients are covered when both criteria are met:

1. The patient has a personal history of melanoma AND:
    a. Either:
        i. Has Stage T1b and above OR
        ii. Has T1a with documented concern about adequacy of microstaging
    b. Is undergoing workup or being evaluated for treatment, AND
    c. Does not have metastatic disease AND
    d. Presumed risk for a positive Sentinel Lymph Node Biopsy (SLNB) based on clinical, histological, or other information is >5% AND
    e. Has a disease stage, grade, and Breslow thickness (or other qualifying conditions) within the intended use of the test
2. The TEST has demonstrated, as part of a Technical Assessment:
    a. Clinical validity of analytes tested in predicting metastatic disease in peer-reviewed scientific literature
    b. Utility beyond clinical, histological, and radiographical factors in the ability to accurately stratify patients into risk groups to manage patient care
    c. Appropriate analytical validity
    d. Performance characteristics equivalent to other covered, similar tests

### Summary of Evidence

Cutaneous melanoma (CM) is increasing in incidence in the U.S., with an estimated 96,480 cases expected to be diagnosed in 2019 with 7,230 deaths.[1]

In the treatment of CM, the risk that a patient has or will develop metastatic disease is central to many of the decision management choices in cutaneous melanoma, with more aggressive management or treatment strategies

recommended for patients who are at a higher risk.[2] 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.[2,3] Patients with a positive SLN are at substantially increased risk for distant metastatic disease and death,[4] however, the procedure only provides prognostic information, and the MSLT-II study showed no survival benefit associated with completion lymphadenectomy in SLN positive patients.[5] 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[6-8]. 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.[9-11] 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.[12] Overall, the likelihood of a positive SLN after the SLNB procedure is 16%,[4,13] but this is variable for specific populations.[13-16] 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,[14-18] which indicates that the prognostic value of SLNB is limited in this population.[19,20] In general, a 5% likelihood for a positive SLN is recommended as a threshold for performing this procedure in a patient population.[13]

Molecular diagnostic tests have been proposed to help managing clinicians risk stratify patients for selecting their most appropriate management based on their probability of developing metastatic disease; these tests may score patients' probabilities of resultant metastatic disease by measuring tumor biomarkers such as relevant gene expression.[21-24] One gene expression profile (GEP) test (DecisionDx Melanoma, Castle Biosciences) was evaluated in a retrospective cohort (n=782) to evaluate its ability to predict metastasis and ability to predict. SLNB status with tumors with a Breslow thickness <2.0 mm (AJCC T1 T2).[25]

The ability of the test to identify a low risk group was assessed and compared to SLNB in two contemporary, multi-center, prospective study cohorts: a 584 patient cohort from two published prospective studies (overall 14% SLN positive rate)[23,26] and a 837 patient cohort from prospectively tested patients at 5 large academic institutions (overall 12% SLN positive rate).[25] 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 were determined to be low risk by this test, the concordance of a negative SLNB was 98.4%. These studies showed improved performance in other patient groups as well.

SLNB positivity rates for T3 tumors with a low risk score for this test is 8.7% Importantly, the 5-year melanoma specific survival (MSS) rate for T1/T2 low risk group remains favorable; with 99% MSS, comparable to that observed in T1a tumors and for which current guidelines do not recommend SLNB.[2,27] Furthermore, T1/T2 low risk patients show 5-year overall survival (OS) of 97% and distant metastasis free survival (DMFS) of 93%.[28]. The MSLT-II study demonstrated that a delay in lymph node dissection does not adversely affect survival, thus clinical follow up of low-risk patients and lymphadenectomy for those few who develop clinically detectable nodal disease should achieve similar outcomes to those who currently undergo a planned SLNB.[5] 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 an MSS survival rate of 99% in those patients with low-risk tumor biology who can safely avoid the procedure.

Clinical validation of this same test as a prognostic test for CM patients was performed in three multicenter, prospectively designed archival tissue studies including 782 patients.[21,22,24] 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. A study focused on patients with melanoma of the head and neck (H&N) has been recently published. Patients with H&N melanoma have poorer outcomes and lower rates of SLN positivity which makes the prognostic value of the SLNB procedure limited and thus additional prognostic information provided by this test is important in this group of patients.[28] Four prospective, independent studies (n= 510) and an interim analysis of two prospective registries (n=322) have confirmed the prognostic accuracy of the assay.[23,29-32] This suggests that the test may be useful in stratifying risk and patient treatment decisions.

A recent retrospective study directly compared the ability of DecisionDx Melanoma with the ability of American Joint Committee on Cancer (AJCC) melanoma staging to predict longer term outcomes.[33] This study looked at 205 archived formalin-fixed, paraffin-embedded primary melanoma tissue blocks from 6 centers. This included 109 Stage I and 96 Stage II cancers, and median time to follow-up was 6.9 years. The median time to recurrence was 1.7 years, and the median time to distant metastasis was 1.6 years. In general, the test scoring alone had greater sensitivity to recurrence, distant metastasis, and death than AJCC staging. Alternatively, AJCC staging had greater specificity for these outcomes. The use of this assay with AJCC staging had a higher sensitivity to these adverse outcomes than either prognostic measurement alone. Lastly, a number of recent studies have suggested that clinicians value and use this test in their medical decision making regarding aggressiveness of melanoma management.[34-36]

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

For cutaneous melanoma, a well-established set of clinical pathways is available for the management of cutaneous melanoma, which are heavily based on risk stratification of patients with higher risk patients being recommended to have a more intense diagnostic workup or more intensive treatment. While the consensus guidelines also give specific clinical, pathologic, and imaging findings that can help to risk stratify a patient, additional evidence suggests that molecular diagnostic tests can be used to further improve risk stratification, thereby improving the accuracy of the risk stratification that is key to deciding on the optimal patient management plan in these clinical pathways. This is particularly the case for identifying the patients at a higher risk of adverse outcomes as a result of the melanoma. As such, tests such as the one evaluated above are considered reasonable and necessary for indications where it has both shown an ability to enhance accuracy of risk stratification and where this risk stratification may be used to select among a number of different consensus recommended management approaches.

Since the clinical utility of this test is dependent upon consensus-based management recommendations based on risk, this coverage decision is subject to change pending changes in the consensus recommended use of risk strata for patient management and the accuracy of alternative risk-stratification tools. This coverage decision will be periodically re-evaluated.

# General Information

**Associated Information**

N/A

**Sources of Information**

N/A

**Bibliography**


1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA: a cancer journal for clinicians.* 2019;69(1):7-34.
2. NCCN Melanoma Panel. *Cutaneous Melanoma Version 1.2019.* November 1 2018.
3. Wong SL, Faries MB, Kennedy EB, et al. Sentinel Lymph Node Biopsy and Management of Regional Lymph Nodes in Melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Clinical Practice Guideline Update. *J Clin Oncol.* 2018;36(4):399-413.
4. Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med.* 2014;370(7):599-609.
5. Faries MB, Thompson JF, Cochran AJ, et al. Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma. *N Engl J Med.* 2017;376(23):2211-2222.
6. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy. *N Engl J Med.* 2016;375(19):1845-1855.
7. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. *Lancet Oncol.* 2015;16(5):522-530.
8. Long GV, Hauschild A, Santinami M, et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. *N Engl J Med.* 2017;377(19):1813-1823.
9. Ascha M, Ascha MS, Gastman B. Identification of Risk Factors in Lymphatic Surgeries for Melanoma: A National Surgical Quality Improvement Program Review. *Ann Plast Surg.* 2017;79(5):509-515.
10. Bagaria SP, Faries MB, Morton DL. Sentinel node biopsy in melanoma: technical considerations of the procedure as performed at the John Wayne Cancer Institute. *Journal of surgical oncology.* 2010;101(8):669-676.
11. Moody JA, Ali RF, Carbone AC, Singh S, Hardwicke JT. Complications of sentinel lymph node biopsy for melanoma - A systematic review of the literature. *Eur J Surg Oncol.* 2017;43(2):270-277.
12. Agnese DM, Abdessalam SF, Burak WE, Jr., Magro CM, Pozderac RV, Walker MJ. Cost-effectiveness of sentinel lymph node biopsy in thin melanomas. *Surgery.* 2003;134(4):542-547; discussion 547-548.
13. Han D, Zager JS, Shyr Y, et al. Clinicopathologic predictors of sentinel lymph node metastasis in thin melanoma. *J Clin Oncol.* 2013;31(35):4387-4393.
14. Cavanaugh-Hussey MW, Mu EW, Kang S, Balch CM, Wang T. Older age is associated with a higher incidence of melanoma death but a lower incidence of sentinel lymph node metastasis in the SEER databases (2003–2011). *Annals of surgical oncology.* 2015;22(7):2120-2126.
15. Sinnamon AJ, Neuwirth MG, Yalamanchi P, et al. Association between patient age and lymph node positivity in thin melanoma. *JAMA dermatology.* 2017;153(9):866-873.
16. Sondak VK, Taylor JM, Sabel MS, et al. Mitotic rate and younger age are predictors of sentinel lymph node positivity: lessons learned from the generation of a probabilistic model. *Ann Surg Oncol.* 2004;11(3):247-258.
17. Balch CM, Soong S-j, Gershenwald JE, et al. Age as a prognostic factor in patients with localized melanoma and regional metastases. *Annals of surgical oncology.* 2013;20(12):3961-3968.
18. Balch CM, Thompson JF, Gershenwald JE, et al. Age as a predictor of sentinel node metastasis among patients with localized melanoma: an inverse correlation of melanoma mortality and incidence of sentinel node metastasis among young and old patients. *Annals of surgical oncology.* 2014;21(4):1075-1081.
19. Fleming NH, Tian J, Vega-Saenz de Miera E, et al. Impact of age on the management of primary melanoma patients. *Oncology.* 2013;85(3):173-181.
20. Macdonald JB, Dueck AC, Gray RJ, et al. Malignant melanoma in the elderly: different regional disease and

poorer prognosis. *J Cancer.* 2011;2:538-543.
21. Gerami P, Cook RW, Russell MC, et al. Gene expression profiling for molecular staging of cutaneous melanoma in patients undergoing sentinel lymph node biopsy. *J Am Acad Dermatol.* 2015;72(5):780-785 e783.
22. Gerami P, Cook RW, Wilkinson J, et al. Development of a prognostic genetic signature to predict the metastatic risk associated with cutaneous melanoma. *Clin Cancer Res.* 2015;21(1):175-183.
23. Hsueh EC, DeBloom JR, Lee J, et al. Interim analysis of survival in a prospective, multi-center registry cohort of cutaneous melanoma tested with a prognostic 31-gene expression profile test. *J Hematol Oncol.* 2017;10(1):152.
24. Zager JS, Gastman BR, Leachman S, et al. Performance of a prognostic 31-gene expression profile in an independent cohort of 523 cutaneous melanoma patients. *BMC Cancer.* 2018;18(1):130.
25. Vetto JT, Hsueh EC, Gastman BR, et al. Guidance of sentinel lymph node biopsy decisions in patients with T1-T2 melanoma using gene expression profiling. *Future Oncol.* 2019;15(11):1207-1217.
26. Dillon LD, Gadzia JE, Davidson RS, et al. Prospective, multicenter clinical impact evaluation of a 31-gene expression profile test for management of melanoma patients. *SKIN The Journal of Cutaneous Medicine.* 2018;2(2):111-121.
27. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin.* 2017;67(6):472-492.
28. Gastman BR, Zager JS, Messina JL, et al. Performance of a 31-gene expression profile test in cutaneous melanomas of the head and neck. *Head Neck.* 2019;41(4):871-879.
29. Greenhaw BN, Zitelli JA, Brodland DG. Estimation of Prognosis in Invasive Cutaneous Melanoma: An Independent Study of the Accuracy of a Gene Expression Profile Test. *Dermatol Surg.* 2018;44(12):1494-1500.
30. Keller J, Schwartz TL, Lizalek JM, et al. Prospective validation of the prognostic 31-gene expression profiling test in primary cutaneous melanoma. *Cancer Med.* 2019;8(5):2205-2212.
31. Podlipnik S, Carrera C, Boada A, et al. Early outcome of a 31-gene expression profile test in 86 AJCC stage IB-II melanoma patients. A prospective multicentre cohort study. *J Eur Acad Dermatol Venereol.* 2019;33(5):857-862.
32. Renzetti M, Farma J, Handorf E, et al. Combined Experience of Two Tertiary Referral Centers with MelanomaDx GEP Testing. Paper presented at: ANNALS OF SURGICAL ONCOLOGY2017.
33. Ferris LK, Farberg AS, Middlebrook B, et al. Identification of high-risk cutaneous melanoma tumors is improved when combining the online American Joint Committee on Cancer Individualized Melanoma Patient Outcome Prediction Tool with a 31-gene expression profile–based classification. *Journal of the American Academy of Dermatology.* 2017;76(5):818-825. e813.
34. Berger AC, Davidson RS, Poitras JK, et al. Clinical impact of a 31-gene expression profile test for cutaneous melanoma in 156 prospectively and consecutively tested patients. *Curr Med Res Opin.* 2016;32(9):1599-1604.
35. Farberg AS, Glazer AM, White R, Rigel DS. Impact of a 31-gene Expression Profiling Test for Cutaneous Melanoma on Dermatologists' Clinical Management Decisions. *J Drugs Dermatol.* 2017;16(5):428-431.
36. Schuitevoerder D, Heath M, Cook RW, et al. Impact of Gene Expression Profiling on Decision-Making in Clinically Node Negative Melanoma Patients after Surgical Staging. *J Drugs Dermatol.* 2018;17(2):196-199.
37. Cook RW, Middlebrook B, Wilkinson J, et al. Analytic validity of DecisionDx-Melanoma, a gene expression profile test for determining metastatic risk in melanoma patients. *Diagnostic pathology.* 2018;13(1):13.
38. Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. *Med Decis Making.* 1991;11(2):88-94.
39. Centers for Disease Control and Prevention. ACCE Model List of 44 Targeted Questions Aimed at a Comprehensive Review of Genetic Testing. 2010. Accessed 10/22/2020.

# Revision History Information

| REVISION HISTORY DATE | REVISION HISTORY NUMBER | REVISION HISTORY EXPLANATION | REASON(S) FOR CHANGE |
|---|---|---|---|
| 12/06/2020 | R4 | **CMS National Coverage Policy** removed the regulation CMS On-Line Manual, Publication 100-02, Medicare Benefit Policy Manual, Chapter 15, §§80.0, 80.1.1, 80.2. Clinical Laboratory services.<br><br>**Bibliography** corrected the link in reference #39.<br><br>Typographical errors were corrected throughout the LCD.<br><br>*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.* | • Provider Education/Guidance |
| 12/06/2020 | R3 | This LCD version was created as a result of DL37750 being released to a Final LCD. | • Creation of Uniform LCDs With Other MAC Jurisdiction |
| 11/01/2019 | R2 | The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD.<br><br>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. | • Other (The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD.<br>) |
| 11/01/2019 | R1 | As required by CR 10901, all billing and coding information has been moved to the companion article, this article is linked to the LCD.<br><br>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 |

# Associated Documents

**Attachments**

N/A

**Related Local Coverage Documents**

Article(s)
A57268 - Billing and Coding: MolDX: Melanoma Risk Stratification Molecular Testing
A58507 - Response to Comments: MolDX: Melanoma Risk Stratification Molecular Testing
LCD(s)
DL37750 - MolDX: DecisionDx-Melanoma

**Related National Coverage Documents**

N/A

**Public Version(s)**

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# Keywords

N/A