MEDICAL POLICY

MEDICAL POLICY DETAILS	
Policy Number	**Gene Expression Profiling for Cutaneous Melanoma**
Policy Number	**2.02.52**
Category	**Technology Assessment**
Original Effective Date	**08/20/20**
Committee Approval Date	**08/20/20, 09/16/21, 09/15/22, 09/21/23**
Current Effective Date	**09/21/23**
Archived Date	**NA**
Archived Review Date	**NA**
Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.* • *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.* • *If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.* • *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.*

POLICY STATEMENT

I. Based upon our criteria and assessment of the peer-reviewed literature, gene expression testing, including but not limited to, the **Pigmented Lesion Assay (PLA)**, in the evaluation of patients with suspicious pigmented lesions is considered **investigational**.

II. Based upon our criteria and assessment of the peer-reviewed literature, gene expression testing, including but not limited to, the **myPath Melanoma test**, in the evaluation of patients with melanocytic lesions with indeterminate histopathologic features is considered **investigational**.

III. Based upon our criteria and assessment of the peer-reviewed literature, gene expression testing, including but not limited to, the **DecisionDx Melanoma test**, in the evaluation of patients with cutaneous melanoma is considered **investigational**.

POLICY GUIDELINES

The Pigmented Lesion Assay, myPath Melanoma, and DecisionDx Melanoma tests are cleared for marketing by the U. S. Food and Drug Administration (FDA). Each is available under the auspices of the Clinical Laboratory Improvement Act (CLIA). Clinical laboratories may develop and validate tests in-house (laboratory-based tests, or LDTs) and market them as a laboratory services. LDTs must meet the general regulatory standards of the CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing.

DESCRIPTION

The DermTech Pigmented Lesion Assay (PLA)

The PLA test measures expression of six genes (PRAME, INC00518, CMIP, B2M, ACTB, and PPIA). The test is performed on skin samples of lesions at least 5 mm in diameter obtained via noninvasive, proprietary adhesive patch

biopsies of a stratum corneum specimen. The test does not work on the palms of hands, soles of feet, nails, or mucous membranes, and it should not be used on bleeding or ulcerated lesions. The PLA test report includes two results. The first result is called the PLA MAGE (Melanoma Associated Gene Expression), which indicates low-, moderate-, or high-risk. The second result is as an algorithmic PLA score that ranges from 0 to 100, with higher scores indicating higher suspicion of malignant disease. Positive PLA tests should be followed-up with a surgical biopsy, while a negative test result allows for monitoring the lesion over time.

The Myriad myPath Melanoma test

The myPath test measures expression of 23 genes using quantitative reverse-transcription polymerase chain reaction. Fourteen genes are involved in melanoma pathogenesis and are grouped into three components related to cell differentiation, cell signaling, immune response, and nine housekeeper genes are also included. The test is performed on five standard tissue sections from an existing formalin-fixed, paraffin-embedded biopsy specimen. The myPath test report includes an algorithmic myPath score ranging from -16.7 to 11.1, with higher, positive scores indicating higher suspicion of malignant disease. The myPath report also classifies these scores: -16.7 to -2.1 are considered "benign"; -2.0 to -0.1 are considered "indeterminate"; and 0.0 to +11.1 are considered "malignant."

The Castle Biosciences DecisionDx-Melanoma test

The DecisionDx-Melanoma test measures expression of 31 genes using quantitative, reverse-transcription, polymerase chain reaction. The test includes 28 prognostic gene targets and three endogenous control genes. The test is performed on standard tissue sections from an existing formalin-fixed, paraffin-embedded biopsy, or wide local-excision specimen. The DecisionDx test report provides two results: a class and probability score. The class results stratify tumors as low-risk (class 1) or high-risk (class 2), with subclassifications within each class (A or B) based on how close the probability score is to the threshold between class 1 and class 2. The probability score ranges from zero to one and appears to be the risk of recurrence within five years.

RATIONALE

For individuals who have suspicious pigmented lesions (based on ABCDE and/or ugly duckling criteria) that are being considered for biopsy and who receive gene expression profiling (GEP) with the DermTech PLA to determine which lesions should proceed to biopsy, the evidence includes observational studies. The relevant outcomes are overall survival (OS), disease-specific survival, validity, and resource utilization. The PLA has one clinical validity study with many methodologic and reporting limitations. Therefore, performance characteristics are not well-characterized. Also, the test has not been compared with dermoscopy, another tool frequently used to make biopsy decisions. No direct evidence of clinical utility was identified. Given that the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility through a chain of evidence. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have melanocytic lesions with indeterminate histopathologic features and who receive GEP with the myPath Melanoma Assay added to histopathology to aid in the diagnosis of melanoma, the evidence includes observational studies. The relevant outcomes are overall survival (OS), disease-specific survival (DSS), test validity, change in disease status, and treatment-related morbidity. The myPath Melanoma Assay has one clinical validity study, which includes long-term follow-up for metastasis as the reference standard. However, it is not clear whether the study population included lesions that were indeterminate following histopathology and the study had other methodologic and reporting limitations as well. Therefore, performance features are not well-characterized. No direct evidence of clinical utility was identified. Given that the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility through a chain of evidence. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are classified as having American Joint Committee on Cancer (AJCC) stage I or II cutaneous melanoma and who receive GEP with the DecisionDx-Melanoma test to inform management decisions regarding enhanced surveillance, the evidence includes retrospective observational studies. The relevant outcomes are OS, disease-specific survival, test validity, change in disease status, resource utilization and treatment-related morbidity. Three reported five-year relapse-free survival (RFS) in AJCC stage I or II patients. Gerami et al (2015) reported RFS rates of 37% for DecisionDx class 2 (high-risk) in patients in AJCC stage I and II patients combined. Zager et al (2018) reported

RFS rates of 85% (95% CI, 74% to 97%) for DecisionDx-Melanoma class 2 patients in AJCC stage 1 and 55% (95% CI, 44% to 69%) for DecisionDx-Melanoma class 2 in AJCC stage II disease. RFS does not appear to be well-characterized, as evidenced by the variation in estimates across studies. This indication is to "rule-in" patients for enhanced surveillance; therefore, specificity and positive predictive value (PPV) are key performance characteristics. Zager et al (2018) and Greenhaw et al (2018) reported specificity of 71% and 87%, respectively, while the PPV was 48% and 24%, respectively. The PPV suggests that most patients identified as high-risk by the DecisionDx test would not develop metastasis and would be unnecessarily subjected to additional surveillance. Greenhaw et al (2018) also reported that, in 219 AJCC stage I patients, 201 had DecisionDx-Melanoma class 1 (low-risk) scores and 18 had DecisionDx-Melanoma class 2 (high-risk) scores. Only one metastasis in stage I patients occurred in a patient with a DecisionDx-Melanoma class 1 score. Therefore, none of the stage 1 patients benefited from DecisionDx-Melanoma testing; 18 (8%) were incorrectly identified as high-risk for metastasis and could have received unnecessary surveillance. There is no evidence that changes to the frequency and methods for surveillance improve outcomes. Given that the evidence is insufficient to demonstrate test performance, and there is no evidence that changes in surveillance improve outcomes, no inference can be made about clinical utility through a chain of evidence. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cutaneous melanoma with clinically negative sentinel lymph node basins that are being considered for sentinel lymph node biopsy (SLNB), and who receive GEP with the DecisionDx-Melanoma test to determine whether to perform SLNB, the evidence includes retrospective observational studies. The relevant outcomes are OS, DSS, test validity, change in disease status, resource utilization and treatment-related morbidity. Three independent clinical validity studies of the DecisionDx-Melanoma test have reported five-year RFS in AJCC stage I or II patients. Gerami et al (2015) reported RFS rates of 98% in DecisionDx-Melanoma class 1 (low-risk) without CIs, in AJCC stage I and II patients. Zager et al (2017) reported RFS rates of 96% (95% CI, 94% to 99%) for DecisionDx-Melanoma class 1 in patients with AJCC stage I disease; they also reported RFS rates of 74% (95% CI, 60% to 91%) for DecisionDx-Melanoma class 1 in patients with AJCC stage II disease. Although CIs were not available for the first study, RFS does not appear to be well-characterized as evidenced by the variation in estimates across studies. Zager et al (2017) also reported that in 56 patients who were DecisionDx-Melanoma class 1 (low-risk) but SLNB-positive, 22 recurrences (39%) occurred over five years. If the DecisionDx-Melanoma test were used as a triage for SLNB, these patients would not undergo SLNB and would likely not receive adjuvant therapy, which has shown to be effective at prolonging time to recurrence in node-positive patients. No direct evidence of clinical utility was identified. Given that the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility through a chain of evidence. The evidence is insufficient to determine the effects of the technology on health outcomes.

National Comprehensive Cancer Network (NCCN) Guidelines (v.2.2023)

- Diagnostic testing for indeterminate melanocytic neoplasms following histopathology guidelines:
  - Melanocytic neoplasms of uncertain biologic potential present a unique challenge to the pathologists and treating clinicians. The Guidelines noted that the ancillary methods to aid in benign versus malignant melanocytic neoplasms included immunohistochemistry (IHC), and molecular testing via comparative genomic hybridization (CGH), fluorescence in situ hybridization (FISH), gene expression profiling (GEP), single-nucleotide polymorphisms (SNP) array, and next generation sequencing (NGS). These tests may facilitate interpretation of cases that are diagnostically uncertain or controversial by histopathology. Ancillary tests should be used as adjuncts to clinical and expert dermatopathological examination and therefore be interpreted within the context of these findings.

- Prognostic testing guidelines:
  - Commercially available GEP tests are marketed as being able to classify cutaneous melanoma into separate categories based on metastasis. However, it remains unclear whether these tests provide clinically actionable prognostic information when used in addition to or in comparison with known clinicopathologic factors or multivariable nomograms that incorporate patient sex, age, tumor location and thickness, ulceration, mitotic rate, lymphovascular invasion, microsatellites, and sentinel lymph node biopsy (SLNB) status. Furthermore, the impact of these tests on treatment outcomes or follow-up schedules has not been established.

- Various (mostly retrospective) studies of prognostic GEP testing suggest its role as an independent predictor of worse outcome, though not superior to Breslow thickness or SLN status. It remains unclear whether available GEP platforms are reliably predictive of outcome across the risk spectrum of melanoma. Prospective validation studies (as have been performed in breast cancer) are required to more accurately define the clinical utility of molecular testing prior to widespread implementation of GEP for prognostication of cutaneous melanoma, and to determine its role in guiding surveillance imaging, SLNB, and adjuvant treatment decisions. Existing and emerging GEP platforms and other prognostic techniques should also be compared with optimized contemporary multivariable phenotypic models (i.e., the AJCC).

American Academy of Dermatology (2019)
Guidelines of Care for the Management of Primary Cutaneous Melanoma (CM):

- Diagnostic GEP test guidelines:
  - Molecular techniques are still largely investigative and may be appropriate as ancillary tests in equivocal melanocytic neoplasms, but they are not recommended for routine diagnostic use in CM. These include comparative genomic hybridization, fluorescence in situ hybridization, gene expression profiling (GEP), and (potentially) next-generation sequencing. Ancillary diagnostic molecular techniques (e.g., CGH, FISH, GEP) may be used for equivocal melanocytic neoplasms.
- Prognostic GEP tests guidelines:
  - There is also insufficient evidence of benefit to recommend routine use of currently available prognostic molecular tests, including GEP, to provide more accurate prognosis beyond currently known clinicopathologic factors" (Strength of evidence: C, Level of evidence II/III). Going forward, GEP assays should be tested against all known histopathologic prognostic factors and contemporary eighth edition of American Joint Committee on Cancer (AJCC) CM staging to assess their additive value in prognostication. Routine molecular testing, including GEP, for prognostication is discouraged until better use criteria are defined. The application of molecular information for clinical management (e.g., sentinel lymph node eligibility, follow-up, and/or therapeutic choice) is not recommended outside of a clinical study or trial.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

CPT Codes

Code	Description
81479	Unlisted molecular pathology procedure
81529 **(E/I)**	Oncology (cutaneous melanoma), mRNA, gene expression profiling by real-time RT-PCR of 31 genes (28 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk, including likelihood of sentinel lymph node metastasis (Decision Dx®- Melanoma, Castle Biosciences, Inc)
81599	Unlisted multianalyte assay with algorithmic analysis
84999	Unlisted chemistry procedure
0089U **(E/I)**	Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es) (Pigmented Lesion Assay (PLA), DermTech)

Code	Description
0090U **(E/I)**	Oncology (cutaneous melanoma) mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin embedded (FFPE)tissue, algorithm reported as a categorical result (i.e., benign, indeterminate, or malignant) (myPath Melanoma, Myriad Genetic Laboratories)
0314U **(E/I)**	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 35 genes (32 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical result (i.e., benign, intermediate, malignant) (DecisionDx DiffDx- Melanoma, Castle Biosciences, Inc)

HCPCS Codes

Code	Description
None	

ICD10 Codes

Code	Description
Z12.83	Encounter for screening for malignant neoplasm of skin
Z80.8	Family history of malignant neoplasm of other organs or systems
C43.0-C43.9	Malignant neoplasm of skin (code range)
C4A.0-C4A.9	Merkel cell carcinoma (code range)
C44.0-C44.99	Other and unspecified malignant neoplasm of skin (code range)
D03.0-D03.9	Melanoma in situ (code range)
D04.0-D04.9	Carcinoma in situ of skin (code range)
L81.0-L81.9	Other disorders of pigmentation (code range)

REFERENCES

Arnot SP, et al. Utility of a 31-gene expression profile for predicting outcomes in patients with primary cutaneous melanoma referred for sentinel node biopsy. Am J Surg 2021 Jun;221(6):1195-1199.

Brouha B, et al. Genomic atypia to enrich melanoma positivity in biopsied lesions: gene expression and pathology findings from a large U.S. Registry study. Skin 2021;5(1):13-18.

Brouha B, et al. Real-world utility of a non-invasive gene expression test to rule out primary cutaneous melanoma: a large US registry study. J Drug Dermatol 2020;19(3):243-249.

Dillon LD, et al. Expanded evidence that the 31-gene expression profile test provides clinical utility for melanoma management in a multicenter study. Curr Med Res Opin 2022 Aug;38(8):1267-1274.

Dillon LD, et al. Prospective, multicenter clinical impact evaluation of a 31-gene expression profile test for management of melanoma patients. Skin 2018;2(2):111-121.

Ferris LK, et al. Noninvasive analysis of high-risk driver mutations and gene expression profiles in primary cutaneous melanoma. J Invest Dermatol 2019 May;139(5):1127-1134.

Ferris, LK, et al. Real-world performance and utility of a noninvasive gene expression assay to evaluate melanoma risk in pigmented lesions. Melanoma Res 2018 Jul 14;28(5).

Fried L, et al. Technological advances for the detection of melanoma: advances in molecular techniques. J Am Acad Dermatol 2020 Oct;83(4):996-1004.

Gastman, BB, et al. Identification of patients at risk of metastasis using a prognostic 31-gene expression profile in subpopulations of melanoma patients with favorable outcomes by standard criteria. J Am Acad Dermatol 2018 Aug 7;80(1).

Gastman, BB, et al. Performance of a 31-gene expression profile test in cutaneous melanomas of the head and neck. Head Neck 2019 Jan 30;41(4).

*Gerami P, et al. Development of a prognostic genetic signature to predict the metastatic risk associated with cutaneous melanoma. Clin Cancer Res Jan 1 2015;21(1):175-183.

Greenhaw, BB, et al. Estimation of Prognosis in Invasive Cutaneous Melanoma: An Independent Study of the Accuracy of a Gene Expression Profile Test Dermatol Surg 2018 Jul 12;44(12).

Greenhaw BN, et al. Molecular risk prediction in cutaneous melanoma: a meta-analysis of the 31-gene expression profile prognostic test in 1,479 patients. J Am Acad Dermatol 2020 Sep;83(3):745-753.

Grossman D, et al. Prognostic gene expression profiling in cutaneous melanoma identifying the knowledge gaps and assessing the clinical benefit. JAMA Dermatol 2020 Jul 29 [Epub ahead of print].

Hornberger J and Siegel DM. Economic analysis of a noninvasive molecular pathologic assay for pigmented skin lesions. JAMA Dermatol 2018;154(9):1025-1031.

Hsueh EC, et al. Long-term outcomes in a multicenter, prospective cohort evaluating the prognostic 31-gene expression profile for cutaneous melanoma. JCO Precision Oncology 2021;5: 589-601.

Hyams DM, et al. Integrating the melanoma 31-gene expression profile test with surgical oncology practice within national guideline and staging recommendations. Future Oncol 2021 Feb;17(5):517-527.

Ko JS, et al. Correlation of melanoma gene expression score with clinical outcomes on a series of melanocytic lesions. Hum Pathol 2018 Dec 20.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Cutaneous Melanoma. Version 2.2023. [https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma_blocks.pdf] Accessed 07/19/23.

Podlipnik, SS, 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 Feb 1.

Reimann, JJ, et al. Comparison of melanoma gene expression score with histopathology, fluorescence in situ hybridization, and SNP array for the classification of melanocytic neoplasms. Mod Pathol 2018 Jun 30;31(11).

Swetter, SS, et al. Guidelines of care for the management of primary cutaneous melanoma. J Am Acad Dermatol 2018 Nov 6;80(1).

Vetto, JJ, et al. Guidance of sentinel lymph node biopsy decisions in patients with T1-T2 melanoma using gene expression profiling. Future Oncol 2019 Jan 30.

Whitman ED, et al. Integrating 31-gene expression profiling with clinicopathologic features to optimize cutaneous melanoma sentinel lymph node metastasis prediction. JCO Precision Oncology 2021 Sep;5:1466-79.

Yousaf A, et al. Validation of CP-GEP (Merlin assay) for predicting sentinel lymph node metastasis in primary cutaneous melanoma patients: a U.S. cohort study. Int J Dermatology 2021 Jul;60(7):851-56.

Zager JS, et al. Performance of a prognostic 31-gene expression profile in an independent cohort of 523 cutaneous melanoma patients. BMC Cancer Feb 5 2018;18(1):130.

*Key Article

KEY WORDS

Pigmented Lesion Assay, myPath Melanoma, and DecisionDx Melanoma

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently no National Coverage Determination (NCD) or Local Coverage Determination (LCD) for gene expression analysis for melanoma management. However, effective 02/10/19 the Medicare Part-B carrier for Arizona, Noridian Healthcare Solutions, LLC, established a Local Coverage Decision for the Molecular Diagnostic Tests for the Decision Dx®-Melanoma test. This covers most of Medicare beneficiaries in all 50 states since Castle Biosciences laboratory in Phoenix, AZ, is within the sole jurisdiction of NHIC for purposes of Part-B coverage. Please refer to:

https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=37748&ver=24&CntrctrSelected=351*1&Cntrctr=351&s=5&DocType=1&bc=AAQAAAIAIAAAAAAA&=+ Accessed 07/19/23.