MEDICAL POLICY

Excellus
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Medical Policy Title	**Gene Expression Profiling for Cutaneous Melanoma**
Policy Number	**2.02.52**
Current Effective Date	**October 16, 2025**
Next Review Date	**October 2026**

Our medical policies are based on the assessment of evidence based, peer-reviewed literature, and professional guidelines. Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. (Link to Product Disclaimer)

POLICY STATEMENT(S)

I. Gene expression profiling (GEP) tests in the evaluation of melanoma (e.g., cutaneous, ambiguous melanocytic or suspicious pigmented lesions) is considered **investigational**, including but not limited to the following tests:

   A. Pigmented Lesion Assay (PLA);

   B. MyPath Melanoma test;

   C. DecisionDx Melanoma test;

   D. DecisionDx DiffDx- Melanoma

RELATED POLICIES

Corporate Medical Policy

11.01.03 Experimental or Investigational

POLICY GUIDELINE(S)

I. The Health Plan and its employees adhere to all State and Federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test or in compliance with applicable law.

II. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.

III. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.

IV. 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

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.

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.”

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.

DecisionDx DiffDx Melanoma Test

DecisionDx DiffDx Melanoma test uses artificial intelligence-based technology to identify 32 genes along with three control genes to classify melanocytic lesions. Two proprietary algorithms are applied to the gene expression pattern to identify the potential malignancy of the lesion.

SUPPORTIVE LITERATURE

Stassen et al (2023) conducted a multicenter prospective study to evaluate the clinical utility of the Clinicopathologic and Gene Expression Profile (CP-GEP) in patients with melanoma who are eligible for sentinel lymph node biopsy (SLNB). The study was conducted on 260 patients with T1–T4 melanoma, the CP-GEP model demonstrated a high negative predictive value of 96.7%, indicating strong reliability in identifying patients unlikely to have nodal metastasis. The positive predictive value was 23.7%, and the model showed potential to reduce SLNB procedures by 42.2% in patients with T1–T3 melanoma. With a median turnaround time of 16 days for test results, the model proved feasible for integration into clinical workflows. These findings support the CP-GEP model as a valuable tool for guiding SLNB decisions in melanoma care. One limitation noted was that the study was in four centers dedicated to melanoma, which may have led to a relatively homogeneous study population.

Amaral et al (2023) conducted a blinded, retrospective, single-center cohort study to evaluate the prognostic value of a clinicopathologic and gene expression profiling model (CP-GEP) in stage I/II cutaneous melanoma, including a subgroup of stage I/IIA patients. The study included 543 patients (stage I: 301; stage II: 242), all of whom underwent sentinel lymph node biopsy (SLNB), and a separate analysis of 80 patients without SLNB. CP-GEP identified 311 high-risk patients with a hazard ratio (HR) of 4.73, capturing 83 of 98 relapses. In the stage I/IIA subgroup, CP-GEP significantly stratified patients with an HR of 3.53 for five-year relapse-free survival (RFS), with RFS rates of 77.8% for high-risk and 93.0% for low-risk patients. Compared to AJCC low-risk patients (86.0% RFS), CP-GEP identified 195 high-risk patients with worse outcomes (77.8% RFS). Among the 80 patients without SLNB (85% stage IA, 90% non-ulcerated tumors), CP-GEP identified 11 high-risk individuals, capturing 6 of 7 relapses, though five-year survival endpoints were not reached. These findings suggest CP-GEP may improve risk stratification in stage I/IIA melanoma, support adjuvant therapy decisions, and potentially serve as an alternative to SLNB.

Greenhaw et al (2020) conducted a meta-analysis that evaluated the prognostic performance of the 31-gene expression profile (31-GEP) test in 1,479 patients with cutaneous melanoma. Five-year recurrence-free and distant metastasis-free survival rates were 91.4% and 94.1% for Class 1A patients and 43.6% and 55.5% for Class 2B patients. The study found that the 31-GEP test effectively stratified patients into low-risk (Class 1) and high-risk (Class 2) categories for metastasis and melanoma-specific mortality. Patients classified as Class 2 had significantly worse outcomes, with higher hazard ratios for recurrence and distant metastasis compared to Class 1. These findings were consistent across multiple independent cohorts, with a sensitivity of 76%. Importantly, the 31-GEP test provided prognostic information beyond traditional staging systems like the AJCC, particularly in early-stage melanoma, supporting its clinical utility in guiding personalized surveillance and treatment strategies.

Marchetti et al (2020) conducted a systematic review and meta-analysis evaluating the prognostic performance of gene expression profile (GEP) tests in patients with localized cutaneous melanoma, particularly those with AJCC stage I and II disease. The analysis included multiple studies including 1450 participants assessing commercially available GEP assays, such as DecisionDx-Melanoma. Among the 623 participants that used DecisionDX-Melanoma with stage I disease, the test correctly identified recurrence in only 29% of cases (6 true positives out of 21 total recurrences), while accurately identifying non-recurrence in 90% of cases (541 true negatives out of 602 non-

recurrences). In contrast, among 212 patients with stage II disease, the test demonstrated higher sensitivity, correctly identifying 82% of recurrences (59 true positives out of 72), but lower specificity, correctly identifying only 44% of non-recurrences (62 true negatives out of 140). These findings suggest that while the test may be more effective in identifying high-risk patients in stage II melanoma, its utility in stage I disease is limited due to low sensitivity. While GEP tests are increasingly used in clinical practice to stratify recurrence risk, the findings revealed that their prognostic accuracy is limited—especially in stage I melanoma, where recurrence rates are low, and test sensitivity is suboptimal. The study concluded that current evidence does not support the routine use of GEP testing as a standalone tool for clinical decision-making in early-stage melanoma. Instead, GEP results should be interpreted cautiously and in conjunction with established clinicopathologic factors.

Pigmented Lesion Assay

Thomsen et al (2023) conducted a systematic review exploring the diagnostic accuracy of tape stripping (TS) as a non-invasive method for identifying malignant melanoma (MM) in suspicious pigmented skin lesions. MM is an extremely aggressive skin cancer, and current diagnostic practices often lead to unnecessary excisions, increasing patient burden and healthcare costs. TS involves collecting epidermal cells using adhesive patches to analyze genetic markers. The review included ten studies, with sensitivity ranging from 68.8% to 100% and specificity from 69.1% to 100%. A pooled analysis of five studies focusing on RNA markers LINC00518 and PRAME showed a sensitivity of 86.9% and specificity of 82.4%. Despite promising results, the overall quality of the studies was low, and further independent research is needed to validate TS as a reliable diagnostic too.

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.

PROFESSIONAL GUIDELINE(S)

National Comprehensive Cancer Network (NCCN) Guidelines: Melanoma: Cutaneous V.2.2025

- Diagnostic testing for indeterminate melanocytic neoplasms following histopathology 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.
- “Based on the current evidence, the NCCN Melanoma Panel does not recommend incorporation of commercially available GEP tests into melanoma care. The use of GEP according to specific AJCC-8 melanoma stage (before or after SLNB) requires further prospective investigation in

large, contemporary datasets of unselected patients. Since there is a low probability of metastasis in stage IA melanoma and a high proportion of false-positive results using these tests, GEP testing should not guide clinical decision-making in this subgroup."

- "Predictive GEP testing to differentiate melanomas at low versus high risk for nodal metastasis should not replace surgical oncology discussion of pathologic staging procedures with SLNB in eligible patients."

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, 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.

REGULATORY STATUS

Not Applicable

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

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
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 Melanoma Test], DermTech, LLC)
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, Castle Biosciences, Inc.)
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)
0578U (E/I)	Oncology (cutaneous melanoma), RNA, gene expression profiling by real- time qPCR of 10 genes (8 content and 2 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reports a binary result, either low-risk or high-risk for sentinel lymph node metastasis and recurrence (Effective 10/01/25)

HCPCS Codes

Code	Description
Not Applicable	

ICD10 Codes

Code	Description
Z12.83	Encounter for screening for malignant neoplasm of skin

Code	Description
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)

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SEARCH TERMS

Not Applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

There is currently no National Coverage Determination (NCD) or Local Coverage Determination (LCD) for gene expression analysis for melanoma management.

MolDX: Melanoma Risk Stratification Molecular Testing (LCD L37748) [accessed 2025 Jul 29]

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, 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 HISTORY/REVISION	
Committee Approval Dates	
08/20/20, 09/16/21, 09/15/22, 09/21/23, 10/17/24, 10/16/25	
Date	**Summary of Changes**
10/16/25	• Annual review; policy intent unchanged
01/01/25	• Summary of changes tracking implemented.
08/20/20	• Original effective date