Regence

**Medical Policy Manual** Genetic Testing, Policy No. 29

# *Gene Expression Profiling for Melanoma*

**Effective**: August 1, 2026

**Next Review:** April 2027
**Last Review:** June 2026



## DESCRIPTION

Gene expression assays have been created to aid risk stratification in patients with melanoma or pigmented lesions suspected of being melanoma.

## MEDICAL POLICY CRITERIA

**Note:** Clinical documentation to support criteria is required (See Required Documentation)

### Medically Necessary

I. The DecisionDx-UM™ gene expression assay may be considered **medically necessary** for individuals with primary, localized uveal melanoma.

### Investigational

II. The DecisionDx-UM™ gene expression assay is considered **investigational** for individuals that do not meet criterion I.

III. All other gene expression assays for melanoma are considered **investigational**, including but not limited to DecisionDX-Melanoma™, Dermtech™ Melanoma Test, AMBLor®, and myPath Melanoma™.

*NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.*

## REQUIRED DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- Name of the genetic test(s) or panel test
- Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
- The exact gene(s) and/or mutations being tested
- Relevant billing codes
- Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
- Medical records related to this genetic test
    - History and physical exam
    - Date of blood draw for test
    - Conventional testing and outcomes
    - Conservative treatment provided, if any

## CROSS REFERENCES

1. Genetic Testing for Cutaneous Malignant Melanoma, Genetic Testing, Policy No. 08
2. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
3. Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer, Genetic Testing, Policy No. 42
4. Investigational Gene Expression, Biomarker, and Multianalyte Testing, Laboratory, Policy No. 77
5. Skin Lesion Imaging and Spectroscopy, Medicine, Policy No. 174

## BACKGROUND

### CUTANEOUS MELANOMA

Cutaneous melanoma represents less than 5% of skin malignancies but results in the most skin cancer deaths. The incidence of cutaneous melanoma continues to increase, and it is currently the sixth most common cancer in the United States. Standard treatment for stage 1 and 2 melanoma is excision with or without sentinel lymph node examination. Current risk factors to predict localized tumor aggression include Breslow tumor thickness, tumor ulceration, and mitotic rate of the tumor cells. Regional lymph node involvement, the likelihood of which increases with increasing tumor thickness, significantly negatively impacts the rate of survival.

### UVEAL MELANOMA

Uveal melanoma, also referred to as ocular or choroidal melanoma, is the most common, but rare, primary ocular malignancy in adults and shows a strong tendency for metastases to the liver. Approximately four million cases of uveal melanoma occur each year.[1] Even with successful treatment of the primary tumor, up to 50% of individuals subsequently develop systemic metastases, with liver involvement in up to 90% of these individuals. Despite aggressive systemic treatments, metastatic liver disease remains the most common cause of tumor-related mortality in choroidal malignant melanoma, with a median survival time of two to seven months and a one-year survival rate of less than 10%. The primary clinical issue in the management of uveal melanoma is accurately predicting risk of metastasis.

Identifying patients at high risk for metastatic disease might assist in selecting patients for adjuvant treatment and more intensive surveillance for metastatic disease, if such changes lead to improved outcomes. The optimal method and interval for surveillance are not well-defined, and it has not been established in prospective trials whether surveillance identifies metastatic disease earlier. Potential methods for metastases include magnetic resonance imaging, ultrasound, liver function testing, and positron emission tomography scans.

## COMMERCIALLY AVAILABLE TESTING

The DermTech™ Melanoma Test (previously called the Pigmented Lesion Assay [PLA] test) measures expression of six genes (*PRAME*, *LINC00518*, *CMIP*, *B2M*, *ACTB*, *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 should not be used on bleeding or ulcerated lesions. The test report includes two results. The first is the MAGE (Melanoma Associated Gene Expression), which indicates low risk (neither *PRAME* nor *LINC00518* expression was detected), moderate risk (expression of either *PRAME* or *LINC00518* was detected), or high risk (expression of both *PRAME* and *LINC00518* was detected). The second result is as an algorithmic score that ranges from 0 to 100, with higher scores indicating higher suspicion of malignant disease. It is not clear whether the test is meant to be used as a replacement, triage, or add-on test with respect to dermoscopy.

The Myriad myPath® test measures expression of 23 genes. Fourteen genes are involved in melanoma pathogenesis and are grouped into three components related to cell differentiation, cell signaling, and the immune response, and nine housekeeping genes are also included. The test is performed on five standard tissue sections from an existing formalin-fixed, paraffin-embedded biopsy specimen, and the 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 classifies these scores: -16.7 to -2.1 are “benign”; -2.0 to -0.1 are “indeterminate”; and 0.0 to +11.1 are “malignant”.

The DecisionDx-Melanoma™ is a gene expression profile test that is a signature of 31 genes, 28 discriminating genes, and three control genes. The test is used to measure risk of metastasis in patients with stage 1 and 2 cutaneous melanoma and classifies tumors into two groups of risk of metastasis, high or low (Class 1 and 2, respectively). The test purports to give an independent prediction of risk of tumor metastatic risk, independent of currently used metrics of risk assessment (e.g., Breslow’s thickness, ulceration status, and mitotic rate; American Joint Committee on Cancer stage, sentinel lymph node biopsy [SLNB] status), so that patients with high-risk stage 1 or 2 disease can possibly undergo more aggressive surveillance treatment than they would have otherwise received.

The Clinicopathological and Gene Expression Profile (CP-GEP, Skyline Dx), also known as the Merlin Assay, uses a combination of gene expression profiling, age, and Breslow thickness to classify patients as either low risk or high risk for metastasis. Eight genes are included in the GEP: *ITGB3*, *PLAT*, *SERPINE2*, *GDF15*, *TGFBR1*, *LOXL4*, *CXCL8* and *MLANA*. This assay has been proposed to identify which patients at low risk that do not need to undergo SLNB.

The DecisionDx-UM™ test (Castle Biosciences Inc.) is a commercially marketed gene expression profiling test intended for use in assessing metastatic risk in individuals with this condition. It consists of a 15-gene polymerase chain reaction (PCR)-based assay that stratifies individuals with uveal melanoma into two classes based on the molecular signature of tumor tissue. Uveal melanomas cluster into two molecular groups based on their gene expression profile. Tumors with the Class 1 signature rarely metastasize, whereas those with the Class 2 signature metastasize at a high rate. Class 1 tumors have been further distinguished into Class 1a (lowest metastatic risk) and Class 1b (moderate long-term metastatic risk).

The manufacturer's website has suggested that physicians can use DecisionDx-Melanoma™ information to guide decisions regarding:

1. "Whether to perform a sentinel lymph node biopsy surgical procedure for eligible patients 55 years of age and older who have tumors less than 2 mm deep (T1 to T2)."

2. "Deciding what level of follow-up, imaging, and referrals are appropriate for any patient with a tumor at least 0.3 mm deep."

## REGULATORY STATUS

The DecisionDx tests are performed in a Clinical Laboratory Improvement Amendment (CLIA)-certified laboratory and do not require U.S. Food and Drug Administration (FDA) clearance.

Note: Microarray-based gene expression analysis of prostate cancer and breast cancer are addressed in separate medical policies (see Cross References).

# EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[2] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. Analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. Clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. Clinical utility, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Review of the literature focused on identifying evidence related to clinical validity and clinical utility, particularly whether the tests can be used to improve treatment planning compared with the standard of care, and whether their use results in improved health outcomes.

## EVALUATION OF SUSPICIOUS PIGMENTED LESIONS

### DermTech™ Melanoma Test

Primary care providers evaluate suspicious pigmented lesions to determine who should be referred to dermatology. Factors considered include both a patient's risk for melanoma as well as a visual examination of the lesion. The visual examination assesses whether the lesion has features suggestive of melanoma. Criteria for features suggestive of melanoma have been developed. One checklist is the ABCDE checklist:[3]

- Asymmetry;
- Border irregularities;
- Color variegation;
- Diameter ≥6 mm;
- Evolution.

Another criterion commonly used is the "ugly duckling" sign.[4] An ugly duckling is a nevus that is obviously different from others in a given patient. Primary care providers generally have a low threshold for referral to dermatology.

Melanoma is difficult to diagnose based on visual examination, and the criterion standard for diagnosis is histopathology. There is a low threshold for excisional biopsy of suspicious lesions for histopathologic examination due to the procedure's ease and low risk as well as the high probability of missing melanoma. However, the yield of biopsy is fairly low. The number of biopsies performed to yield one melanoma diagnosis has been estimated to be about 15 for U.S. dermatologists.[5] Therefore a test that could accurately identify those lesions not needing a biopsy (i.e., a rule-out test for biopsy) could be clinically useful. The purpose of gene expression profiling (GEP) in patients who have suspicious pigmented lesions being considered for biopsy is to inform a decision about whether to biopsy.

**Clinical Validity**

Studies were excluded from the evaluation of the clinical validity of the DermTech™ Melanoma Test (previously called the Pigmented Lesion Assay) because they reported results of the development cohort,[6] they did not use the marketed version of the test,[6, 7] did not include the reference standard test on test-negative patients,[8] did not adequately describe the patient characteristics,[9] or did not adequately describe patient selection criteria.[9]

The validation cohort from the Gerami (2017) publication was included.[10] This was a retrospective study that included lesions that were selected by dermatologists experienced in pigmented lesion management from 28 sites in the United States, Europe, and Australia; therefore, the samples were likely not consecutive or random. Information regarding the previous testing was not provided. The flow of potential and included samples was not clear, and neither was whether the samples were all independent or if multiple samples from the same patient were included. Diagnosis of melanoma was based on consensus among a primary reader and three expert dermatopathologists. The report did not state whether the histopathologic diagnosis was blinded to the results of the DermTech™ test but did state the diagnosis was "routinely" assessed. Interpretation of the test result does not depend on a reader, so it is blinded to histopathologic results. In 11% of cases originally selected, a consensus diagnosis was not reached, and these samples were not included in the training or validation cohorts. Dates of data collection were not reported. Sex and anatomic location of biopsy were reported, but other clinical characteristics (e.g., risk factors for melanoma, presenting symptoms) were not. The study training cohort included 157 samples with 80 melanomas and 77 nonmelanomas. The study validation cohort included 398 samples with 87 melanomas (22%) and 311 non-melanomas. The sensitivity and specificity of the test in this group was 91% (95% confidence interval [CI] 83% to 96%) and 69% (95% CI 64% to 74%), respectively, yielding a positive predictive value (PPV) of 45% (95% CI 38% to 53%) and a negative predictive value (NPV) of 96% (95% CI 93% to 98%).

### Clinical Utility

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. No direct evidence of clinical utility was identified.

A decision-impact study by Ferris (2017) assessed the potential impact of the DermTech™ test on physicians' biopsy decisions for patients.[9] Forty-five dermatologists evaluated 60 clinical and dermoscopic images of atypical pigmented lesions (8 melanoma, 52 nonmelanoma). In the first round, dermatologists did not have DermTech™ test results, and in the second round, dermatologists had access to the test results with the order of cases being scrambled. The dermatologists were asked whether the lesions should be biopsied after each round. Therefore, the corresponding number of biopsy decisions should be 45×60×2=5,400. Data were collected in 2014 and 2015. Results were reported for 4,680 decisions with no description of the disposition of the remaining decisions. Of the 4,680 reported decisions, 750 correct biopsy decisions were made without the DermTech™ test results while 1,331 were made with the test results, and 1,590 incorrect biopsy decisions were made without test results while 1,009 incorrect biopsy decisions were made with the results.

## GEP FOR DIAGNOSING LESIONS WITH INDETERMINATE HISTOPATHOLOGY

### MyPath

The purpose of GEP testing in patients whose melanocytic lesion is indeterminate after histopathology is to aid in the diagnosis of melanoma and decisions regarding treatment and surveillance. In cases of indeterminate histopathology, long-term follow-up is needed to determine evaluate the clinical outcome, specifically metastasis.

Development of the myPath test was described by Clarke (2015).[11] The myPath test is meant to be used as an add-on test to standard histopathology. Studies have evaluated the performance characteristics of the test when histopathology is used as the reference standard,[11-13] but are not the focus of this evidence review given that the test's potential usefulness is in evaluation of indeterminate lesions.

Studies were excluded from the evaluation of the clinical validity of the myPath test because authors did not use the specified reference standard of long-term (at least five years) follow-up[11-16] and/or did not adequately describe patient characteristics.

The clinical validity study by Ko (2017) met selection criteria.[17] For this study, archived melanocytic neoplasms were submitted for myPath testing from university clinics in the United States and United Kingdom with additional samples acquired from Avaden BioSciences. Stage 1, 2, and 3 primary cutaneous melanomas that produced distant metastases subsequent to the diagnosis and benign lesions with clinical follow-up and no evidence of recurrence of metastases were included. For benign samples, a disease-free time of at least five years was recommended. Information on the previous testing was not provided. It is not clear if any of the samples originally had indeterminate histopathology results. Dates of data collection were not reported. Sex, age, Breslow depth, and anatomic location were described; presenting symptoms were not reported. A total of 293 samples were submitted; of these 53 did not meet inclusion criteria and 58 (24% of those tested) failed to produce a valid test score. An additional seven samples with indeterminate results were excluded from the calculations of performance characteristics. Of the remaining 175 samples, 54 were diagnosed as melanoma with metastases. The sensitivity and specificity of the test in this group was 94% (95% CI 87% to 98%) and 96% (95% CI 89% to 99%), respectively, with a PPV of 97% (95% CI 91% to 99%) and an NPV of 93% (95% CI 85% to 97%). A limitation of the study is that it was not limited to lesions that were indeterminate following histopathology. In addition, the samples were not consecutive or random, and it is unclear how much time elapsed between the biopsy and the myPath test. A follow-up analysis by Clarke (2020) was limited to lesions with "diagnostic uncertainty" from this study.[18] Of the 125 lesions that met diagnostic uncertainty criteria, 54 were determined to be malignant based on clinical outcomes and 47 (87%) of these had a "likely malignant" test result.

### Clinical Utility

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. No direct evidence of clinical utility was identified.

Two decision-impact studies assessed the potential impact of myPath on physicians' treatment decisions in patients with diagnostically challenging lesions.[19, 20] Given the lack of established clinical validity and no reported long-term health outcomes, it is not known whether any treatment changes were clinically appropriate.

## CUTANEOUS MELANOMA

Many treatments and surveillance decisions are determined by a patient's prognostic stage group based the American Joint Committee on Cancer tumor, node, metastasis staging system. The prognostic groups are as follows: stage 1, T1a through T2a primary melanomas without evidence of regional or distant metastases; stage 2, T2b through T4b primary melanomas without evidence of lymphatic disease or distant metastases; stage 3: pathologically documented involvement of regional lymph nodes or in transit or satellite metastases (N1 to N3); stage 4: distant metastases. Patients may also SLNB to gain more definitive information about the status of the regional nodes. Wide local excision is the definitive surgical treatment of melanoma. Following surgery, patients with American Joint Committee on Cancer stage 1 or 2 (node-negative) melanoma do not generally receive adjuvant therapy. Patients with higher risk melanoma receive adjuvant immunotherapy or targeted therapy. Patients with stage I and IIA disease should undergo an annual routine physical and dermatologic examination. These patients typically do not receive surveillance imaging. Patients with stage 2B – stage 3 melanoma may be managed with more frequent follow-up and imaging surveillance following therapy. However, follow-up strategies and intervals are not based on rigorous data, and opinions vary regarding appropriate strategies.

The purpose of GEP in patients with melanoma is to identify low and high-risk patients classified as stage 1 or 2 according to the American Joint Committee on Cancer (AJCC) criteria. Current guidelines do not recommend adjuvant therapy or imaging surveillance for AJCC stage 1 or 2 patients following surgery. Patients initially staged as 1 or 2 who have positive lymph nodes following SLNB are then eligible to be treated with adjuvant therapy as stage 3 patients.

**DecisionDX-Melanoma™**

<u>Clinical Validity</u>

*Systematic Reviews*

Durgham (2024) collected data from 13 studies, comprising of 14,760 individuals, and conducted a meta-analysis to provide a comprehensive assessment of the current evidence of DecisionDx test's prognostic performance.[21] Critical appraisal of these studies using the Begg's test and Egger's regression test indicated an overall low risk of bias with the potential sources of bias attributed to study confounding, attrition, and participation. Relevant survival outcomes, based on the natural history of melanoma, for the GEP classes were assessed using a random effects estimates model to account for the confounding heterogeneity and variability of the studies used. The five-year melanoma-specific survival (MSS) rate for the overall population was 97.5% (95% CI 86.5 to 99.6). Additional survival-related outcomes (three-year overall survival, three-year recurrence-free survival, three-year distant metastasis-free survival, and five-year MSS) were assessed and demonstrated better outcomes for Class 1 and 1A compared to Class 2 and 2B. Although this meta-analysis provided a consensus of the current literature for relevant survival outcomes of interest there are still some notable limitations of this review, including but not limited to, a small number of studies available for GEP class per outcome, heterogeneity among studies, and the lack of information on study treatments used during the studies. Additionally, the GEP test's categorization conflicts with the Melanoma Prevention Working Group’s recommendations for GEP tests to be reported as continuous variables. Further evidence via randomized-control trials evaluating long-term outcomes of patients with GEP-informed testing is necessary to further define the possible role of the DecisionDx test in the management of patients with melanoma.

*Observational Studies*

Several papers were excluded from the evaluation of clinical validity of the DecisionDx™ test. Hsueh (2017), Podlipnik (2019), Hsueh (2021), Bailey (2023), Guenther (2025) were excluded from the evaluation because they did not report five-year outcomes.[22-26] Samples used in Gerami (2015)[27] and Ferris (2017)[28] appear to overlap with the samples from Gerami (2015)[29] and each other and will not be considered independent validation studies for inclusion in the table. They are described briefly following the clinical validity tables. Samples used in both papers by Gastman (2019) are stated to overlap previous validation studies.[30, 31] Vetto (2019) included a retrospective cohort that was used to develop the model and is thus not eligible for inclusion, as well a prospective cohort with some overlapping samples and without report of five-year outcomes.[32] A publication by Marks (2019) describes the development of a cutpoint.[33]

Four independent clinical validity studies meeting eligibility criteria have been conducted. Characteristics and results are summarized in Tables 1 and 2 and briefly in the paragraphs that follow.

**Table 1. Clinical Validity Study Characteristics of the DecisionDx-Melanoma Test for Diagnosing Melanoma**

| Study | Study Population | Design | Outcome Measure | Threshold for Positive Test | Timing | Assessor Blinding |
|---|---|---|---|---|---|---|
| Gerami (2015);[29] Validation subset | Adults<br>Stage I-IV cutaneous melanoma (87% stage I/II) At least 5 y of FU (median, 7.0 y)<br>Median Breslow thickness, 0.8 mm (nonmetastasis) and 3.99 mm (metastasis)<br>SLN positivity NR | Retrospective<br>Not consecutive or randomly selected | 5-y RFS | Class 2 is high-risk<br>Risk threshold not provided | Patient diagnosed between 1998 and 2009<br>Timing of DecisionDx not described | Yes |
| Zager (2018)[34] | Stage I-III cutaneous melanoma (68% stage I/II)<br>At least 5 y of FU (median, 7.5 y)<br>Median Breslow thickness, 1.2 mm<br>30% SLN positive | Retrospective<br>Not consecutive or randomly selected | 5-y RFS | Class 2 = high risk<br>Class 1 probability score 0-0.49<br>Class 2 probability score 0.5-1 | Patients diagnosed between 2000 and 2014<br>Timing of DecisionDx not described | Yes |
| Greenhaw (2018)[35] | Patients who were treated for primary invasive CM of any Breslow depth within the last 5 years and had had GEP testing (86% stage I, 14% stage II)<br>Mean follow-up of 23 months; only 20 patients had 5-year follow-up | Retrospective<br>Consecutive | 5-y MFS | Commercial test cutoffs used | Institution offered DecisionDx testing to newly diagnosed and those treated within the previous five years | Yes |

| Study | Study Population | Design | Outcome Measure | Threshold for Positive Test | Timing | Assessor Blinding |
|---|---|---|---|---|---|---|
| Keller (2019)[36] | Patients had CM (91% stage I/II), opted for GEP testing and underwent SNB and wide excision of primary tumor. Median follow-up time, 3.5 years Median Breslow thickness, 1.4 mm 9% SLN positive | Prospective | 3-y MFS | Commercial test cutoffs used | Patients diagnosed between 2013 and 2015<br>GEP reported to be performed concurrently with SNB | Yes |

FU: follow-up; RFS: recurrence-free survival; MFS: metastasis-free survival; GEP: gene expression profiling; CM: cutaneous melanoma; SLN: sentinel lymph node; SNB: sentinel node biopsy

### Table 2. Clinical Validity Study Results of the DecisionDx-Melanoma Test for Diagnosing Melanoma

| Study | Initial / Final N | Excluded Samples | Sensitivity, % (95% CI) | Specificity, % (95% CI) | PPV, % (95% CI) | NPV, % (95% CI) |
|---|---|---|---|---|---|---|
| Gerami (2015);[29] Validation subset | | Samples excluded if melanoma dx not confirmed, dissectible area not acceptable | | | | |
| Overall | Unclear / 104 | | 89 (73 to 97)[a] | 83 (72 to 91)[a] | 72 (56 to 85)[a] | 93 (84 to 98)[a] |
| AJCC stage 1 and 2 | Unclear / 78 | | 86 (64 to 97)[a] | 84 (72 to 93)[a] | 67 (46 to 83)[a] | 94 (84 to 99)[a] |
| Zager (2018)[34] | | Did not meet analytic quality control thresholds | | | | |
| Overall | 601 / 523 | | 70 (62 to 78) | 71 (67 to 76) | 48 (41 to 55) | 87 (82 to 90) |
| AJCC stage 1 | Unclear / 264 | | 35 (14 to 62)[a] | 87 (82 to 91)[a] | 15 (6 to 31)[a] | 95 (91 to 98)[a] |
| AJCC stage 2 | Unclear / 93 | | 77 (61 to 89)[a] | 43 (29 to 57)[a] | 49 (36 to 62)[a] | 72 (53 to 86)[a] |
| Greenhaw (2018)[35] | 256 / 256 | None excluded but only 20 had 5-year follow-up | 77 (46 to 94) | 87 (82 to 91) | 24 (13 to 40) | 99 (96 to 100) |

| Study | Initial / Final N | Excluded Samples | Sensitivity, % (95% CI) | Specificity, % (95% CI) | PPV, % (95% CI) | NPV, % (95% CI) |
|---|---|---|---|---|---|---|
| Keller (2019)[36] | 159 / 174 | 15 patients had insufficient tumor for GEP testing | NR | NR | NR | NR |

AJCC: American Joint Committee on Cancer; Dx: diagnosis; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; RFS: recurrence-free survival; MFS: metastasis-free survival

[a] Confidence intervals not provided in the report; calculated from data provided.

The validation cohort in Gerami (2015) included patients with stage 0, 1, 2, 3, or 4 disease from six U.S. centers (n=104).[29] A complete disposition of samples received from the institutions and those included in the analysis was not provided. For 78 patients in the validation cohort with AJCC stage 1 or 2 cutaneous melanoma who had either a metastatic event or had more than five years of follow-up without metastasis, five-year disease-free survival was 98% (CIs not reported) for DecisionDx class 1 patients and 37% for DecisionDx class 2 patients. The PPV and NPV were 67% and 94%, respectively. CIs for performance characteristics were calculated in Table 2 based on data provided

Zager (2018) reported results of a second clinical validity study including AJCC stage 1, 2, or 3 primary melanoma tumors from 16 U.S. sites.[34] The samples were independent of the other validation studies. Of the 601 cases submitted from the institutions, 523 were included in the analysis (357 stage 1 and 2). The excluded samples did not meet pre- and post-analytic quality control thresholds. SLNB status was untested in 36% of the patients, negative in 34%, and positive in 30%. The report did not describe any adjuvant therapy that the patients received. Overall, 42 (13%) recurrence events occurred in DecisionDx class 1 patients and 100 (48%) recurrence events occurred in DecisionDx class 2 patients. The five-year recurrence free survival (RFS) estimated by Kaplan-Meier was 88% (95% CI 85% to 92%) in class 1 and 52% (95% CI, 46% to 60%) in class 2. The reported sensitivity and specificity were 70% (95% CI 62% to 78%) and 71% (95% CI 67% to 76%), respectively, with a PPV of 48% (95% CI 41% to 55%) and a NPV of 87% (95% CI 82% to 90%). For comparison, the performance characteristics for five-year RFS for sentinel lymph node status among those with SLNB were: sensitivity 66% (95% CI 57% to 74%); specificity 65% (95% CI 58% to 71%); PPV 52% (95% CI 44% to 60%); and NPV 76% (95% CI 69% to 82%). Estimates stratified by AJCC stage I or II are shown in Table 2. If DecisionDx were used as a triage test such that only class 2 received SLNB, then 159 class 1 patients would not have undergone SLNB. Of the 159 patients in class 1, 56 were SLNB-positive and were therefore eligible for adjuvant therapy. It is not clear if the SLNB-positive patients in this study received adjuvant therapy. Of the 56 patients who were DecisionDx class 1 and SLNB-positive, 22 recurrence events occurred by five years.

Greenhaw (2018) reported results of an independent study of the DecisionDx test using their institution's melanoma registry and including patients who had been treated for cutaneous melanoma within the last five years and undergone DecisionDx testing.[35] Study characteristics and results were reported in the preceeding Tables 1 and 2. Two-hundred fifty-six patients were tested; 84% were categorized as DecisionDx class 1 (low-risk) and 16% were DecisionDx class 2 (high-risk). Of these, 219 (86%) tumors were AJCC stage I and 37 (14%) were AJCC stage II. None of the 18 stage 1/class 2 tumors metastasized but 1 (0.5%) of 201 stage I/class 1 tumors metastasized. Ten (42%) of the stage 2/class 2 tumors metastasized and 2 (15%) of the 13 stage 2/class 1 tumors metastasized.

Keller (2019) reported results of a validity study including 159 patients (ages 26 to 88) diagnosed with melanoma between 2013 and 2015 who underwent SNB and concurrent GEP testing.[36] Study characteristics and results were reported in the preceding Tables 1 and 2. There were 117 patients classified as class 1 (91 subclass 1A and 26 subclass 1B) and 42 classified as Class 2 (12 subclass 2A and 30 subclass 2B); and 78% of the tumors were AJCC stage 1, 13% were stage 2, and 9% were stage 3. Five-year RFS was reported only in a figure and sample sizes at year five and precision estimates were not included. There were six recurrent events (n=117) in class 1 patients by three years (three-year RFS 97%, 95% CI 93% to 100%). There were 23 recurrent events (n=42) in class 2 patients (three-year RFS 47%, 95% CI 34% to 65%). GEP class was significantly associated with RFS in multivariate analysis controlling for age, Breslow thickness, ulceration and SNB results.

In a subsequent analysis of patients with melanoma who had undergone SLNB, Gerami (2015) compared the prognostic accuracy of GEP and biopsy.[27] Patients who had undergone SLNB appear to overlap with patients in Gerami (2015)[29], discussed previously. Most (73%) patients had a negative SLNB, and 27% had a positive SLNB. DecisionDx-Melanoma classified 76 (35%) tumors as low-risk (class 1) and 141 (65%) tumors as high-risk (class 2). Within the group of SLNB-negative patients, the five-year OS rate was 91% in class 1 patients and 55% in class 2 patients. Within the group of SLNB-positive patients, the five-year OS rate was 77% in class 1 patients and 57% in class 2 patients.

Ferris (2017) compared the accuracy of DecisionDx-Melanoma™ with the web-based AJCC Individualized Melanoma Patient Outcome Prediction Tool.[28] The study included 205 patients who appear to overlap with the patients in the second Gerami (2015) study described above. AJCC-predicted five-year survival for each patient was categorized into low and high-risk based on both a 68% predicted five-year survival and a 79% predicted five-year survival. The 68% and 79% cutpoints were reported to correspond to five-year survival in patients with stage IIA and IIB, respectively, although it is unclear whether those cutpoints were prespecified, whether they were based on internal or external estimates of risk, or whether they are commonly used in practice. The prognostic sensitivity and specificity for death (median follow-up, seven years) of the Decision-Dx Melanoma™ were 78% and 69%, respectively (CIs not reported). The sensitivity and specificity for the AJCC calculator with the 79% cutpoint were 60% and 74%, respectively. The combination of the DecisionDx-Melanoma™ and AJCC tools had a sensitivity of 82% and specificity of 62%.

Pazhava (2024) retrospectively analyzed electronic health records from patients with cutaneous melanoma who underwent GEP testing to evaluate the current clinical utility and performance of the DecisionDx test.[37] The study examined the prognostic performance of the GEP classifications using two survival outcomes: RFS and MSS. The median follow-up for all survival endpoints was 38.7 months, with significant variability in follow-up durations. Clinical utilization was assessed by determining if the GEP test influenced management decisions regarding a patient's melanoma diagnosis. Overall, the GEP classification only affected 18.5% of patients' management decisions with two cases forgoing SNLB, three cases referred to medical oncology, and five cases that had adjusted postdiagnosis surveillance, but ultimately these classifications did not significantly alter treatment decisions or led to better net health outcomes. Kaplan-Meier analysis indicated that survival curves for RFS and MSS between Class 1 versus Class 2 patients were not statistically different.

<u>Clinical Utility</u>

Several decision-impact studies have been published reporting on the impact of DecisionDx-Melanoma on physicians' management decisions.[38-44] Given the lack of established clinical validity and no reported long-term outcomes of the test used to select patients for active surveillance, it is not known whether any management changes were clinically appropriate.

For the proposed use of the test as a triage for SLNB (to identify patients who can avoid SLNB), performance characteristics are not well-characterized. For the proposed use of the test as a replacement for SLNB (identify patients who are AJCC stage 1 or 2 who should receive adjuvant therapy), performance characteristics are also not well-characterized. In addition, an evidence-based management pathway would be needed to support the chain of evidence. The existing RCTs demonstrating that adjuvant therapy reduces recurrence included node-positive patients.

For the proposed use of the test to identify patients who are AJCC stage 1 or 2 who should receive enhanced surveillance, there is also a lack of evidence that imaging surveillance or increased frequency of surveillance improves outcomes in stage 1 and 2 patients. The National Comprehensive Cancer Network guidelines state that imaging surveillance is not recommended for stage 1-2A and can be 'considered' for 2B-4, but that there is an absence of meaningful data on the association of rigorous routine surveillance imaging with improved long-term outcome for stage 2B-2C and the recommendations regarding consideration of imaging surveillance remain controversial. While earlier detection of recurrence is thought to be beneficial because lower tumor burden and younger age are associated with improved treatment response and survival, this has not been proven and RCTs are needed to assess whether enhanced surveillance improves survival. The optimal frequency and duration of follow-up surveillance are not standardized and how the surveillance would be altered for DecisionDx class 2 patients has not be defined.

No evidence was identified that demonstrated that adjuvant therapy or increased surveillance improves net health outcomes in AJCC stage 1 or 2 patients who are DecisionDx class 2.

**Clinicopathological and Gene Expression Profile (CP-GEP, Merlin Test)**

<u>Clinical Validity</u>

*Systematic Reviews*

Wong (2025) conducted a PROSPERO-registered systematic review and meta-analysis of four independent external validation studies of the CP-GEP model (also known as the Merlin Test) published between 2020 and June 2024.[45] The pooled analysis included 1,061 individuals with a pooled median age of 60 years, median Breslow thickness of 1.55 mm, and overall SLNB positivity rate of 17.8%. Quality assessment using the QUADAS-2 tool identified no studies at high risk of bias. The model performed best for pT2 melanomas (n=483, SLNB positivity 14.3%), with pooled sensitivity of 91% (95% CI 82% to 96%), specificity of 35% (95% CI 30% to 39%), NPV of 96% (95% CI 91% to 98%), and SLNB reduction rate of 31% (95% CI, 27% to 35%).  For pT3 melanomas, the SLNB reduction rate was only 3% (95% CI 1% to 6%), indicating minimal utility in this subgroup. For pT1 melanomas, high SLNB reduction rate was observed (72%, 95% CI 55% to 85%) but with wide confidence intervals and substantial heterogeneity, reflecting limited sample size and low SLNB positivity (6.8%). The authors concluded that the CP-GEP model can reduce the number of unnecessary SLNBs performed, particularly in pT2 patients. Notable limitations include, but are not limited to, limited number of studies; blinding between the index test and reference standard not described in two of the studies; substantial heterogeneity in overall (pT1–pT4) pooled estimates for specificity, PPV, and SLNB reduction rate, with insufficient numbers of pT1 and pT4 studies to support reliable subgroup inference; and the absence of individual patient data.

*Nonrandomized Studies*

Four independent external validation studies of the Merlin CP-GEP model were published between 2020 and June 2024 and covered in the systematic review and meta-analysis by Wong (2025), described above. Mulder (2021) reported a model that had an AUC of 0.66 (95% CI 0.59 to 0.74) with 20% of the individuals (42/210) classified as low risk; among these, four (9.5%) had a positive SLNB.[46] Yousaf (2021) evaluated the CP-GEP model in a pre-planned subgroup analysis of patients 65 years or older (n=77) and reported a SLNB reduction rate of 43.1% (95% CI 29.3% to 57.8%) at an NPV of 95.5% (95% CI 77.2% to 99.9%) in the T1–T2 population, suggesting CP-GEP may provide particular value in older patients for whom SLNB is often elective.[47] Johansson (2022) validated the CP-GEP model in 421 consecutive patients and compared it with the MSKCC and MIA nomograms in the pT1–T2 subpopulation (n=358), CP-GEP achieved a higher SLNB reduction rate (34.2% vs. 25.2% MSKCC vs. 0.5% MIA) with comparable NPV (95.7% vs. 96.1% MSKCC vs. 100% MIA).[48] In patients 65 years or older (n=171), the pT1–T3 NPV was 97.6% (95% CI 87.1% to 99.9%) with a SNLB reduction rate of 29.5% (95% CI 22.1% to 37.8%). Stassen (2023) conducted the first prospective multicenter evaluation of the CP-GEP model in a clinical implementation context, evaluating 222 individuals who underwent SNLB with T1b–T4 primary cutaneous melanoma.[49]

Zijlker (2026) reported the CP-GEP assay classified 68 individuals (28%) as low risk and 175 (72%) as high risk, while performing the best in the pT1b–pT2a subgroup (n=132), with an NPV of 93.3% (95% CI 83.8 to 98.2%) and an SLNB reduction rate of 45.5% (95% CI 36.8 to 54.3%).[50] For five-year prognostic outcomes, CP-GEP low-risk patients had a RFS of 89.6% (95% CI 79.5 to 94.9%) versus 76.8% (95% CI 69.8 to 82.4%) for high-risk patients (HR 2.41), distant metastasis-free survival (DMFS) of 95.6% (95% CI 86.9 to 98.5) versus 81.3% (95% CI 74.5 to 86.4, HR: 4.46), and MSS of 98.5% (95% CI 89.9 to 99.8) versus 88.9% (95% CI 83.2 to 92.8 HR 7.88).

Weitemeyer (2025) reported results from a retrospective multicenter cohort (n=536) validation study of the CP-GEP and in a secondary analysis using a 0.3 mm sentinel lymph node tumor burden cutoff to reclassify clinically irrelevant nodal disease, the overall NPV improved to 95.4% (95% CI 91.8 to 97.8%) and T1 NPV to 98.4% (95% CI 94.5 to 99.8%), suggesting that lowering the tumor burden threshold can improve the test performance without compromising the risk of SLN metastasis.[51] Additionally, the CP-GEP model was compared to the MIA nomogram (n=507 evaluable) and classified 42.4% of individuals as low risk (NPV 91.2%) versus 8.1% by MIA (NPV 95.1%).

Pazhava (2025) evaluated CP-GEP performance specifically in 250 individuals with primary cutaneous melanoma of the head and neck region.[52] In T1–T2 melanomas (n=167), the SLNB reduction rate was 56.3% (95% CI 48.4% to 63.9%) at an NPV of 98.9% (95% CI 94.2% to 100%). Among 215 SLNB-negative patients, the CP-GEP assay further stratified outcomes for low-risk patients (n=100) with a five-year RFS of 86.1% compared to 68.1% in high-risk patients (HR 2.49, $p<0.05$), five-year DMFS of 92.7% vs. 75.8% (HR 3.15, $p<0.05$), and five-year MSS of 95.3% vs. 85.5% (HR 2.26, $p=0.175$).

Amaral (2025) evaluated CP-GEP for risk stratification in 930 individuals with clinical stage I/II primary cutaneous melanoma from the University of Tuebingen, Germany, who did not undergo SLNB, with a median follow-up of 165 months. [52,] The CP-GEP assays classified 879 individuals (94.5%) as low risk and 51 (5.5%) as high risk. Low-risk patients had significantly better 10-year RFS (94.5% vs. 37.5%, HR 20.07, p<0.001), 10-years DMFS (98% vs. 70%, HR 19.44, p<0.001), MSS (98.6% vs. 66.8%; HR: 35.85; p<.001), and OS (80.2% vs. 38.4%; HR: 5.59; p<.001) compared with high-risk patients. Limitations include the retrospective single-center design conducted at a German institution with a predominantly Caucasian European population, predominantly thin melanoma (median Breslow thickness 0.50 mm overall; 76.8% T1a), and marked Breslow thickness differences between risk groups (median 0.50 mm for Low Risk vs. 3.60 mm for High Risk), which may substantially drive survival differences independent of the genomic component. No SLNB data were available, and no actionable treatment pathway currently exists for stage I-IIA patients identified as high-risk by CP-GEP.

Hieken (2025) reported results of the MERLIN_001 study, the largest prospective, multicenter, double-blinded evaluation of the CP-GEP test for SLN metastasis risk stratification.[53] Nine U.S. academic medical centers enrolled 1,761 eligible individuals with T1 to T3 cutaneous melanoma and clinically negative regional lymph nodes who elected for SLNB. The Merlin assay classified 651 individuals (37.0%) as low risk and 1,110 (63.0%) as high risk. Among low-risk cases, 46 (7.1%) were SLN positive, yielding an NPV of 92.9% (95% CI 90.7% to 94.8%). Among high-risk cases, 264 (23.8%, 95% CI 21.3% to 26.4%) were SLN positive, a 3.4-fold higher risk. The percentage of cases classified as low risk declined with increasing T category (T1: 68.2%; T2: 32.9%; T3: 2.8%), indicating limited utility in T3 tumors. In the largest subset, patients with clinical stage IB melanoma (n=1,187, 67.4% of the study population), 49.3% were classified as low risk with an observed SLN-positive rate of 6.5% (95% CI 4.6% to 8.8%) compared with 18.3% (95% CI 15.3% to 21.6%) in high-risk cases. The primary study objective, with an upper bound of the 95% CI for SLN positivity in low-risk cases, was not met, as a majority of patients had a >6% risk of sentinel node metastasis. In patients 65 years or older (n=832, 47.2%), 42.1% were classified as low risk with an SLN-positive rate of 6.6% (95% CI 4.2% to 9.7%) compared with 20.3% (95% CI 16.8% to 24.2%) in high-risk cases. Results were consistent across anatomic sites, histologic subtypes, and mitotic count categories. Notable limitations include surgeon-selected enrollment, absence of centralized pathology review, absence of race/ethnicity data, and the absence of health outcome data in the current publication. The test was not recommended to replace SLNB but to inform shared decision-making.

Clinical Utility

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. No direct evidence of clinical utility was identified. For the proposed use of the test as a triage for SLN biopsy (identify patients who can avoid SLN biopsy), performance characteristics are well-characterized as indicated by prospective and retrospective studies. However, given that the primary objective of the double-blinded prospective study conducted by Hieken (2025, discussed above), was not achieved and that a low-risk CP-GEP result does not reduce a patient's sentinel node metastasis risk below the guideline-based threshold for omitting SLNB, no inferences can be made about clinical utility through a chain of evidence.

## UVEAL MELANOMA

### DecisionDX-UM

Clinical Validity

Roelofs (2022) performed a retrospective analysis of 343 patients with uveal melanoma who underwent GEP classification, including 255 patients with class 1 and 88 patients with class 2 results.[54] Patients were classified as being at low (GEP class 1 and tumor thickness <8 mm) or high risk of metastasis (GEP class 2 or tumor thickness ≥8mm); low-risk patients underwent annual surveillance abdominal ultrasound, while high-risk patients underwent alternating surveillance liver ultrasound and abdominal magnetic resonance imaging every six months according to institutional protocol. The mean follow-up was 40 ± 26 months. In univariate Cox proportional hazard regression, enucleation, ciliary body involvement, extraocular extension, tumor thickness, largest basal tumor diameter (as a continuous and categorical [>12mm] variable), and GEP class 2 were associated with future metastasis. Multivariate Cox proportional hazards regression indicated GEP class 2 and longest basal diameter >12mm remained independently predictive of metastasis-free survival, and stratified analysis further indicated longest basal diameter >12mm remained predictive of metastasis-free survival in both GEP class 1 and 2 tumors.

Singh (2022) performed a retrospective analysis of metastasis-free survival in patients with uveal melanoma, with a focused analysis comparing predicted (according to DecisionDx-UM metastasis-free survival prediction for GEP class 2 [i.e., 50% at three years, 28% at five years]), observed (via analysis of a cohort of consecutive patients with uveal melanoma treated at the authors' two institutions), and published (via a meta-analysis of patients with uveal melanoma from seven retrospective or prospective studies utilizing GEP published between 2012 and 2021) metastasis-free survival in GEP class 2 subgroups.[55] The overall retrospective cohort consisted of 343 patients, of whom 121 were GEP class 2, while the meta-analysis pooled data from 667 GEP class 2 patients. In the analysis of GEP class 2 patients, both observed and meta-analysis-derived published metastasis-free survival at three and five years were longer than the corresponding DecisionDx-UM-predicted survival, with point estimate differences ranging from 12% to 19%. The predicted metastasis-free survival estimate was below the lower limit of the 95% confidence interval for both observed and published survival estimates at both time points.

Davanzo (2019) conducted a retrospective review of 107 consecutive uveal melanoma patients, including 39, 31, and 37 patients with unknown, low-, and high-risk GEP results.[56] Low-risk patients were followed with hepatic ultrasonography every six months, whereas high-risk patients were managed with more frequent hepatic imaging. High-risk patients (8/37) were significantly more likely to develop metastasis ($p<0.001$) compared to patients in the low/unknown risk group (0/70) (see Table 3).

Cai (2018) retrospectively evaluated a cohort of 240 patients with uveal melanoma arising from the choroid and/or ciliary body.[57] The study sought to determine whether the prognostic accuracy of combined GEP and PRAME (preferentially expressed antigen in melanoma) status was noninferior to the AJCC tumor-node-metastasis (TNM) staging system for uveal melanoma. Patients were followed for a median duration of 29 months with metastasis as the primary endpoint. GEP class was the most significant predictor of metastasis ($p=1.5\text{x}10^{-8}$). The prognostic accuracy of an optimized GEP/PRAME model ($p=8.6\text{x}10^{-14}$) was superior to an optimized TNM model ($p=1.3\text{x}10^{-5}$).

Augsburger (2015) reported on the correlation between GEP classifications when samples from two sites from the same tumor were tested.[58] This prospective, single-center study enrolled 80 patients who had uveal melanoma resection. Tumor samples were taken from two different sites and GEP testing was performed independently on both samples. The primary measure reported was the rate of discordance between the two samples on GEP Class. Nine (11.3%) cases were definitely discordant (95% CI 9.0% to 13.6%), and 13 (16.3%) cases were definitely or possibly discordant (95% CI 13.0% to 19.6%). Thus, the heterogeneity of tumor and limitations to sampling may explain cases of misclassification where GEP results do not accurately predict prognosis.

Onken (2010) revalidated the GEP assay when it was migrated from a microarray platform to a polymerase chain reaction–based 15-gene assay comprised of 12 discriminating genes and three endogenous control genes from previously published data sets collected from the same group.[59, 60] Technical performance of the assay was assessed in 609 tumor samples, including 553 fine needle aspiration biopsies and 56 enucleation specimens from the authors' laboratory (n=188) and 11 collaborating sites (n=421). According to the study protocol, sample failure rate due to incorrect specimen handling was low, occurring in 32 of 609 (5.3%) of samples (p<0.0001). Preliminary data suggested the potential for increased sensitivity of gene expression profiling compared with cytologic diagnosis, as the assay failed in only one of 51 (2%) of samples with insufficient material for cytological diagnosis; however, point estimates of overall test accuracy (e.g., sensitivity, specificity, or both) were not provided. In a subset of 172 individuals with UM, the relationship between tumor class and metastasis was studied with available clinical data and a median follow-up time of 16 months. Within this group, the assay was reported to correctly identify individuals who went on to develop metastatic disease. Kaplan-Meier analysis showed approximately 24% Class 2 individuals with uveal melanoma surviving at 48 months and close to 100% survival in the Class 1 group, although more specific data was not provided. This study evaluated primarily fine needle aspiration biopsy specimens (553 of 609, or 90.8%) rather than enucleation specimens; however, the data reported on the relationship between tumor class and metastasis are limited, and median follow-up time was reported as a relatively short duration (16 months).

In a prospective, multicenter study by Onken (2012), the prognostic performance of the 15-gene GEP assay was evaluated in 459 patients with posterior uveal melanoma from 12 independent centers.[61] Tumors were classified by GEP as Class 1 or Class 2. The first 260 samples were also analyzed for chromosome 3 status using a single nucleotide polymorphism assay. Net reclassification improvement analysis was performed to compare the prognostic accuracy of GEP with the 7th edition clinical Tumor-Node-Metastasis (TNM) classification and chromosome 3 status. Patients were managed for their primary tumor and monitored for metastasis. The GEP assay successfully classified 446 of 459 cases (97.2%). Metastasis was detected in three Class 1 cases (1.1%) and 44 Class 2 cases (25.9%) (log-rank test, P<10(-14)). At three years follow-up, the net reclassification improvement of GEP over TNM classification was 0.43 (p=0.001) and 0.38 (p=0.004) over chromosome 3 status. The GEP provided a highly significant improvement in prognostic accuracy over clinical TNM classification and chromosome 3 status. The impact of the test results on health outcomes were not identified in the study.

Walter (2016) evaluated two cohorts of patients at two clinical centers who underwent resection for uveal melanoma.[62] This study had similar methodology to Onken (2012) study described above. The primary cohort included 339 patients, of which 132 patients were also included in the Onken study, along with a validation cohort of 241 patients, of which 132 were also included in the Onken study, the latter group of which was used to test a prediction model using the GEP plus pretreatment largest basal diameter. Cox proportional hazards analysis was used in the primary cohort to examine GEP classification and other clinicopathologic factors (tumor diameter, tumor thickness, age, sex, ciliary body involvement, pathologic class).

GEP Class 2 was the strongest predictor of metastases and mortality. Tumor diameter was also an independent predictor of outcomes, using a diameter of 12 mm as the cutoff value. In the validation cohort, GEP results were Class 1 (61.4%) in 148 patients and Class 2 (38.6%) in 93 patients.

Similar outcomes were reported by Demirci (2018) in a retrospective review of 293 patients with choroidal melanoma.[63] Class 2 tumors with largest basal diameter ≥ 12 mm and class 2 and 1B tumors with American Joint Committee on Cancer (AJCC) stage III showed significantly worse prognosis. At a median follow-up of 26 months, the probability of metastasis-free survival was lowest in patients with class 2 tumors (HR 0.60, 95% CI 0.44 to 0.72) compared to patients with class 1A (HR 0.99, 95% CI 0.94 to 0.99) or class 1B (HR 0.90, 95% CI 0.77 to 0.96) tumors. The authors subsequently analyzed a scoring system combining AJCC stage and GEP in the same dataset (including three additional patients since the 2018 publication), with results indicating better estimate of prognosis with the combined score than with use of AJCC stage or GEP alone.[64]

Decatur (2016) published a smaller, retrospective study of 81 patients who had tumor samples available from resections occurring between 1998 and 2014.[65] GEP was Class 1 in 35 (43%) patients, Class 2 in 42 (52%) patients, and unknown in four (5%) patients. GEP Class 2 was strongly associated with BAP1 variants ($r=0.70$, $p<0.001$). On Cox proportional hazards analysis, GEP Class 2 was the strongest predictor of metastases and melanoma mortality.

Corrêa (2016) performed a single-institution prospective intervention case series to compare the prognostic value of the 15-gene GEP test with other conventional prognostic factors for metastasis and metastatic death, including 299 patients with posterior uveal melanoma evaluated by fine-needle aspiration biopsy at the time of or shortly prior to initial treatment.[66] The cohort in this study had a substantial proportion of patients with smaller tumors compared to previous studies, and this was reflected in the higher proportion of Class 1 to Class 2 cases in this cohort; 211 (70.6%) Class 1 patients and 88 (29.4%) Class 2 patients. Stepwise multivariant analysis determined that although GEP class was the strongest prognostic factor for metastatic death in this series; that tumor large basal diameter was also a significant prognostic indicator of metastatic death. Kaplan-Meier survival curves demonstrated lower survival in GEP Class 2 patients compared with Class 1 patients, but survival and metastasis rates by class were not reported.

Field (2016) published a follow-up study of the Onken (2010) validation cohort, looking at additional biomarkers to complement the DecisionDx-UM GEP test results in 389 consecutive patients.[67] This study analyzed 64 tumor samples previously determined as Class 1 in an effort to find independent markers of metastasis in these samples. The investigators reported that Class 2 GEP was associated with significantly greater metastatic risk than Class 1 GEP, with metastatic disease being detected in 12/216 (6%) Class 1 cases versus 63/173 (36%) Class 2 cases ($p<0.0001$).

**Table 3. Studies of Clinical Validity**

| Study | Patient Populations | Rates of Metastases | | Melanoma Mortality Rates | |
|---|---|---|---|---|---|
| | | GEP Class 1 | GEP Class 2 | GEP Class 1 | GEP Class 2 |
| Onken (2012)[61] | 459 pts with UM from 12 clinical centers | 1.1% | 25.9% | NR | NR |
| Walter (2016)[62] | Primary cohort: 339 pts from one clinical center | 5.8% | 39.6% | 3.7% | 29.5% |

| Study | Patient Populations | Rates of Metastases | | Melanoma Mortality Rates | |
|---|---|---|---|---|---|
| | with UM arising in ciliary body or choroid | | | | |
| | Validation cohort: 241 pts from one (different) clinical center with UM arising in ciliary body or choroid | 2.7% | 31.2% | 0.7% | 17.2% |
| Decatur (2016)[65] | 81 pts from a single center with available tumor samples of UM arising in ciliary body or choroid | | 9.4<br>(3.1 to 28.5) | | 15.7%<br>(3.6 to 69.1) |
| Field (2016)[67] | 389 pts from two clinical centers with UM arising in ciliary body or choroid | 6% | 36% | NR | NR |
| Demirci (2018)[63] | 293 patients from 2 clinical centers with UM arising from the choroid | 3.6% | 26.5% | NR | NR |
| Cai (2018)[57] | 240 patients from a single center with UM arising from the choroid and/or ciliary body | 10.2%<br>3.9% (*PRAME*-)<br>6.3% (*PRAME*+) | 41.1%<br>19.6% (*PRAME*-)<br>21.4% (*PRAME*+) | NR | NR |
| Davanzo (2019)[56] | 107 consecutive patients from a single-center with UM | 0% | 21.6% | NR | NR |
| Roelofs (2022)[54] | 343 patients from a single center with non-metastatic UM | 4.3% | 34% | NR | NR |
| Singh (2022)[55] | • Observed survival cohort: 343 consecutive patients from two centers with UM, including 121 GEP class 2 patients<br>• Published survival pooled cohort: 667 GEP class 2 patients | • Observed 3-year MFS: 93% (95% CI 89% to 97%)<br>• Observed 5-year MFS: 87% (95% CI 81% to 93% | 3-year MFS:<br>• Predicted:[c] 50%<br>• Observed: 67% (95% CI 59% to 77%)<br>• Published: 62% (95% CI 57% to 66%)<br><br>5-year MFS:<br>• Predicted:[c] 28%<br>• Observed: 47% (95% CI 37% to 61%)<br>• Published: 40% (95% CI 34% to 46%) | NR | NR |

CI: confidence interval; GEP: gene expression profile; MFS: metastasis-free survival; NR: not reported; *PRAME*: preferentially expressed antigen in melanoma; UM: uveal melanoma

## Clinical Utility

To date, there are no published studies that address the specificity, sensitivity, or positive- and negative-predictive values, and no studies that compare patient health outcomes as a result of patient management with versus without this testing. However, a chain of evidence based on the clinical validity of the test can be developed.

Khan (2022) conducted a multicenter, single-arm study of crizotinib as adjuvant therapy in adults with localized high-risk uveal melanoma (defined as GEP class 2 and longest basal tumor diameter >12mm).[68] This was the first published clinical trial of crizotinib in uveal melanoma. Patients received crizotinib 250 mg by mouth twice daily for a total of 48 weeks, beginning within 90 days of primary enucleation or radiotherapy. The primary outcome was 32-month relapse-free survival (RFS) rate; planned enrollment was 30 patients to provide 90% power to detect a 75% RFS rate at 32 months relative to a 50% RFS rate based on historical data. The analysis included a comparison of the primary outcome in the study cohort to a 2:1 propensity score-matched historical control. Among the 34 patients enrolled, the median age was 60 years, and all patients had an Eastern Cooperative Oncology Group performance status of 0 or 1. The mean relative dose intensity per cycle was 84%; four patients did not complete 48 weeks of treatment with crizotinib due to toxicity despite dose reduction. In 32 evaluable patients, at a median follow-up of 47.1 months, the estimated 32-month RFS rate was 50% (95% CI 23% to 67%). There was no difference in the primary outcome between the study cohort and the propensity score-matched historical control cohort, in whom the estimated 32-month RFS rate was 57% (95% CI 40% to 73%). All patients experienced at least one treatment-related adverse event, the most common of which were nausea, transaminase elevation, diarrhea, fatigue, and sinus bradycardia.

Schefler (2020) reported on risk-appropriate changes in management following testing with DecisionDx-UM in a prospective, multicenter cohort (n=93) enrolled in the Clinical Application of DecisionDx-UM Gene Expression Assay Results (CLEAR II) registry study.[69] Following testing, 44 (98%) of class 2 patients received a referral to another provider, of which 42 (93%) received referrals to medical oncology. For class 1 patients, 55 (59%) received a referral to another provider, of which 47 (51%) were referred to medical oncology. Medical oncology referral was more common for high-risk class 2 patients compared to class 1 ($p<0.001$). Class 2 patients were 3.3 times more likely to receive high-frequency chest imaging ($p<0.001$) and 4.3 times more likely to received high-frequency abdominal imaging ($p<0.001$). Health outcomes resulting from changes in management were not reported.

Plasseraud (2016) reported metastasis surveillance practices and patient outcomes using data from a prospective observational registry study of DecisionDx-UM conducted at four centers, which included 70 patients at the time of reporting.[70] Surveillance regimens were documented by participating physicians as part of registry data entry. “High-intensity” surveillance was defined as imaging and/or liver function testing (LFTs) every three to six months and “low-intensity” surveillance was defined as annual imaging and/or LFTs. The method for following patients for clinical outcomes was not specified. Of the 70 enrolled patients, 37 (53%) were Class 1. Over a median follow-up of 2.38 years, more Class 2 patients (36%) than Class 1 patients (5%; $p=0.002$) experienced metastasis. The three-year metastasis-free survival rate was lower for Class 2 patients (63%; 95% CI 43% to 83%) than Class 1 patients (100%, $p=0.003$). Most Class 1 patients (n=30) had low-intensity surveillance, and all (n=33) Class 2 patients had high-intensity surveillance. Aaberg (2020) published updated five-year outcomes for 89 patients.[71] Of these 89 patients, 49 (55%) were class 1, of which 39 (80%) received low-intensity management. The five-year metastasis-free survival rate was 90% for class 1 patients compared to 40.7% for class 2 patients ($p<0.0001$). The five-year MSS was 94.3% for class 1 patients compared to 63.4% for class 2 patients ($p=0.0007$). Strengths of this study included a relatively large population given the rarity of the condition, and an association between management strategies and clinical outcomes. However, it is not clear which outcome measures were prespecified or how data was collected, making the risk of bias high.

Aaberg (2014) reported on changes in management associated with GEP risk classification.[1] The study analyzed Medicare claims data submitted to Castle BioSciences by 37 ocular oncologists in the United States. Data were abstracted from charts on demographics, tumor pathology and diagnosis, and clinical surveillance patterns. High-intensity surveillance was defined as a frequency of every three to six months and low-intensity surveillance was a frequency of every 6 to 12 months. Of 195 patients with GEP test results, 88 (45.1%) patients had evaluable tests and adequate information on follow-up surveillance, 36 (18.5%) had evaluable tests and adequate information on referrals, and 8 (4.1%) had evaluable tests and adequate information on adjunctive treatment recommendations. Of the 191 evaluable GEP tests, 110 (58%) were Class 1 and 81 (42%) were Class 2. For patients with surveillance data available (n=88), all patients in GEP Class 1 had low-intensity surveillance and all patients in GEP Class 2 had high-intensity surveillance ($p<0.001$ vs. Class 1).

## PRACTICE GUIDELINE SUMMARY

There are no evidence-based clinical practice guidelines which specifically recommend the use of gene expression assays, specifically the DecisionDx assays, to guide the clinical management of patients with malignant tumors.

### NATIONAL COMPREHENSIVE CANCER NETWORK

#### Cutaneous Melanoma

The National Comprehensive Cancer Network guidelines (v.2.2026) for cutaneous melanoma state the following the use of GEP to evaluate lesions of uncertain malignancy following histology:[72]

> "Ancillary tests to differentiate benign from malignant melanocytic neoplasms include IHC [immunohistochemistry] and molecular testing via comparative genomic hybridization (CGH), fluorescence in situ hybridization (FISH), gene expression profiling (GEP), single-nucleotide polymorphism (SNP) array, and next generation sequencing (NGS). These tests may facilitate a more definitive diagnosis and guide therapy in cases that are diagnostically uncertain or controversial by histopathology. Ancillary tests should be used as adjuncts to clinical and expert dermatopathologic examination and therefore be interpreted within the context of these findings."

The guidelines additionally state:

> “Based on the current evidence, the NCCN Melanoma Panel does not recommend incorporation of commercially available prognostic GEP tests into melanoma care. The routine use of GEP to predict patient outcome according to specific AJCC-8 melanoma stage (before or after SLNB) requires further prospective investigation in large, contemporary datasets of unselected patients. Moreover, 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 the subgroup.
>
> Predictive GEP tests to differentiate melanomas at low versus high risk for nodal metastasis should not replace surgical oncology discussion of pathologic staging with SLNB in eligible patients. Findings of the prospective Merlin_001 trial suggest that clinicopathologic (CP)-GEP testing may be used in select patients with T1b ± T2a melanoma to support shared decision-making, when a patient or provider would decide against SLNB if the true risk was <10%. A high-risk result in that scenario would portend a 3 times higher risk of SLN involvement based on trial results. Alternative GEP tests for

SLNB risk prediction are not recommended outside of the context of a clinical study or trial based on current data. Additional prospective investigation and outcomes data (including impact of missing a positive SLNB) will further inform the utility of GEP tests, multivariable nomograms/risk calculators […], and other decision analytical models for SLNB risk prediction. Existing GEP tests for SLNB risk prediction should be prospectively compared with no-cost, contemporary models that incorporate readily available CP variables."

**Uveal Melanoma**

The National Comprehensive Cancer Network (NCCN) guidelines for uveal melanoma (v.2.2026)[73] state: "PRAME expression is a risk modifier to the 15-GEP (gene expression profile) and may be associated with an increased risk of metastasis in both Class 1 and Class2 uveal melanoma tumors."

## AMERICAN ACADEMY OF DERMATOLOGY

The American Academy of Dermatology (2019) published guidelines of care for the management of primary cutaneous melanoma.[74] The guidelines state the following regarding GEP tests:

Regarding diagnostic GEP tests:

- "Diagnostic 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 (eg, CGH, FISH, GEP) may be used for equivocal melanocytic neoplasms."

Regarding prognostic GEP tests:

- "...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 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 (eg, sentinel lymph node eligibility, follow-up, and/or therapeutic choice) is not recommended outside of a clinical study or trial."

## SOCIETY OF SURGICAL ONCOLOGY

The Society of Surgical Oncology published a consensus statement in 2025 regarding the use of GEP to guide management of patients with melanoma, which included the following recommendations:[75]

“Question 1: In adult patients with American Joint Committee on Cancer (AJCC) pT1a-pT4b primary cutaneous melanoma, does GEP testing improve patient selection and decision making for sentinel lymph node biopsy (SLNB) as compared with the use of conventional clinical and pathologic factors alone?

- GEP testing is not currently recommended for routine use in predicting sentinel lymph node (SLN) status. There is a lack of high-level evidence regarding changing indications for SLNB based on GEP results.
- There is currently a lack of high-level evidence that GEP testing improves selection above clinicopathologic factors for SLNB in patients with AJCC pT1a primary cutaneous melanoma.
- High-quality evidence (including prospective, adequately powered studies with independent validation) is desired to assess the role for GEP testing in guiding selection for SLNB in patients with AJCC pT1b-T2 primary cutaneous melanoma.
- There is currently a lack of high-level evidence that GEP testing improves selection for SLNB in patients with AJCC pT3-T4 primary cutaneous melanoma.

Question 2: Does GEP testing improve current risk stratification of adult patients with AJCC pT1a-pT4b primary cutaneous melanoma sufficiently to recommend its utilization to guide decision making for surveillance imaging and follow-up?

- GEP testing is not currently recommended to guide a specific surveillance or follow-up approach in melanoma care.
- GEP testing is not recommended to guide surveillance strategy or follow-up in patients with AJCC pT1a (clinical stage IA) melanoma who have an otherwise excellent prognosis.
- EP testing is not currently recommended to replace SLNB for prognostication or staging, or to guide surveillance and adjuvant treatment approaches in patients (AJCC pT1b-pT4b) who are otherwise recommended for the procedure.

Question 3: In adult patients with primary cutaneous melanoma, does GEP testing provide additional information and improve risk stratification, beyond current diagnostic standards, to influence decisions for the utilization and utility of adjuvant therapy?

- There is currently a lack of evidence supporting the use of GEP testing to inform treatment decisions for the utilization or the utility of adjuvant therapy.”

## MELANOMA PREVENTION WORKING GROUP

The Melanoma Prevention Working Group (2020) published consensus recommendations regarding the use of GEP for cutaneous melanoma.[76] After evaluating the available evidence, the working group concluded that the published evidence is “insufficient to establish that routine use for GEP testing provides additional clinical value for melanoma stating and prognostication beyond available clinicopathologic variables,” and that findings are needed from large, representative patient populations with adequate clinical follow-up to allow comparison with these variables.

## SUMMARY

### Medically Necessary

There is enough research to show that the DecisionDX-UM™ genetic test can identify certain patients with uveal melanoma that are at higher risk for their cancer to spread. This information can be used to help determine how often patients should be checked for metastatic disease. Therefore, the DecisionDX-UM™ genetic test may be considered medically necessary for individuals with primary, localized uveal melanoma.

### Investigational

There is not enough research to show that the DecisionDX-UM™ genetic test can be useful to measure risk in people with other types of disease, including people with uveal cancer that has spread from another site in the body. Therefore, the DecisionDX-UM™ genetic test is considered investigational in people who do not meet the policy criteria.

There is not enough research to show that any other gene expression tests can help to guide patient management and improve health outcomes for people with cutaneous melanoma or pigmented lesions suspected of being melanoma. Therefore, gene expression assays, including but not limited to DecisionDX-Melanoma™, Dermtech™ Melanoma Test, and myPath Melanoma™, are considered investigational in patients with cutaneous melanoma or pigmented lesions.

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## CODES

| Codes | Number | Description |
|---|---|---|
| CPT | 0089U | Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es) |
| | 0090U | Oncology (cutaneous melanoma) mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin embedded tissue, algorithm reported as a categorical result (ie, benign, indeterminate, or malignant) |
| | 0314U | 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 (ie, benign, intermediate, malignant) |
| | 0387U | Oncology (melanoma), autophagy and beclin 1 regulator 1 (AMBRA1) and loricrin (AMLo) by immunohistochemistry, formalinfixed paraffin-embedded (FFPE) tissue, report for risk of progression |
| | 0578U | Oncology (cutaneous melanoma), RNA, gene expression profiling by real-time qPCR of 10 genes (8 content and 2 housekeeping), utilizing formalin-fixed |

| Codes | Number | Description |
|---|---|---|
| | | paraffin-embedded (FFPE) tissue, algorithm reports a binary result, either low-risk or high-risk for sentinel lymph node metastasis and recurrence |
| | 81479 | Unlisted molecular pathology procedure |
| | 81529 | 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 |
| | 81552 | Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis |
| | 81599 | Unlisted multianalyte assay with algorithmic analysis |
| | 84999 | Unlisted chemistry procedure |
| | 88299 | Unlisted cytogenetic study |
| HCPCS | None | |

***Date of Origin:*** *April 2013*