Gene Expression Profile Testing for Melanoma

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COVERAGE CRITERIA 2
POLICY CROSS REFERENCES 3
POLICY GUIDELINES 3
CLINICAL EVIDENCE AND LITERATURE REVIEW 5
HEALTH EQUITY CONSIDERATIONS 15
BILLING GUIDELINES AND CODING 16
REFERENCES 17
POLICY REVISION HISTORY 18

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SCOPE: Providence Health Plan, Providence Health Assurance and Providence Plan Partners as applicable (referred to individually as “Company” and collectively as “Companies”).

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☐ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

Uveal Melanoma: Guideline Note 173, Line 662
Cutaneous Melanoma: Guideline Note 173, Line 662

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

Uveal Melanoma

I. The DecisionDx-UM™ gene expression profile (GEP) test may be considered **medically necessary** in patients with a confirmed diagnosis of primary, localized uveal melanoma with no evidence of metastasis.

II. Gene expression profile test(s) for uveal melanoma are considered **not medically necessary** when criterion I. above is not met, including but not limited to the following:

A. Patients who do not have a confirmed diagnosis of uveal melanoma
B. Patients whose uveal cancer that has spread from another site in the body
C. Patients whose uveal melanoma has already metastasized
D. Use of GEP test other than DecisionDx-UM™

Cutaneous Melanoma

III. Gene expression profile tests for cutaneous melanoma may be considered **medically necessary** for diagnostic testing of indeterminate melanocytic neoplasms (e.g., myPath Melanoma, DiffDx-Melanoma) when histopathology has been performed.

IV. Gene expression profile tests for cutaneous melanoma are considered **not medically necessary** when criterion III. above is not met, including but not limited to the following:

A. To guide initial biopsy decisions (e.g., Pigmented Lesion Assay [PLA])
B. To risk stratify cutaneous melanomas (i.e. prognosis/predictive testing)
C. To determine metastatic risk (e.g., DecisionDx-Melanoma).

V. Repeat testing of the same germline genetic content, for the same genetic information is considered **not medically necessary**.

Link to Evidence Summary

POLICY CROSS REFERENCES

- None.

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

DOCUMENTATION REQUIREMENTS

In order to determine the clinical utility of a genetic test, the following documentation must be provided at the time of the request. Failure to submit complete documentation may affect the outcome of the review.

- Specific gene, trade or proprietary name of the test, or if a custom-built test, include every gene(s) and/or component of the test
- Name of laboratory where the testing is being conducted or was conducted
- Clinical notes to include the following:
  - Reason (indication) for performing test, including the suspected condition
  - Existing signs and/or symptoms related to reason for current test request
  - Prior test/laboratory results related to reason for current test request
  - Family history, if applicable
  - How results from current test request will impact clinical decision making
- All relevant CPT/HCPCS codes billed

BACKGROUND

Uveal (Intraocular) Melanoma

Melanoma of the uveal tract is the most common primary intraocular malignancy in adults. The incidence of uveal melanoma (UM) in the United States is approximately 4.3 new cases per million people, with males having a higher incidence than females. The incidence has been relatively stable of the last 30 years.[1]

Uveal melanomas can arise in the anterior (iris) or the posterior (ciliary body or choroid) uveal tract. Most uveal tract melanomas originate in the choroid, whereas the least common site of origin is the iris. Iris melanomas have the best prognosis, whereas melanomas of the ciliary body have the least favorable prognosis.[1]

There are a number of factors influence prognosis. Important factors include cell type, tumor size, location of the anterior margin of the tumor, degree of ciliary body involvement, and extraocular extension.[1] However, more recently, gene expression profile (GEP) testing has been developed as a means of determining risk of metastasis and aid in the management of UM patients.

Cutaneous Melanoma

Skin cancer is the most common malignancy diagnosed in the United States, with 5.4 million cancers diagnosed in 2012. Melanoma, a malignant tumor of melanocytes, represents about 1% of skin cancers but results in most deaths. Although most melanomas arise in the skin, they may also arise from mucosal surfaces. The incidence has been increasing over the past 30 years, with elderly men being at the highest risk.[2]

Diagnosis of a suspicious lesions includes a biopsy, preferably by local excision, with specimens being examined by an experienced pathologist to allow for microstaging. Of note, studies show that distinguishing between benign pigmented lesions and early melanomas can be difficult, and even experienced dermatopathologists can have differing opinions. Therefore, the development of additional tools, including GEP tests, are currently underway and are proposed to be used as adjuncts to standard clinical and histopathological staging, particularly for indeterminate lesions.

Prognosis is affected by the characteristics of primary and metastatic tumors, with important factors including thickness and/or level of invasion of the melanoma, mitotic index, ulceration or bleeding at the primary site, number of regional lymph nodes involved, and systemic metastasis. Although these factors provide some information for disease management, they have limited predictive power.[3] The development of additional tools, including GEP tests, that may provide more accurate information regarding metastatic risk is, therefore, an area of active research.

Gene Expression Profile (GEP) Tests

DecisionDx-UM (Uveal Melanoma) (Castle Biosciences, Inc.)

According to Castle Biosciences, the DecisionDx-UM test is a gene expression profile (GEP) test that is intended to determine 5-year risk based on the activity or “expression” of 15 genes, as determined by quantitative real-time PCR (qRT-PCR).[4] The DecisionDx-UM prognostic test reports Class 1A, Class 1B and Class 2 phenotype:

- Class 1A: Very low risk, with a 2% chance of the eye cancer spreading over the next five years;
- Class 1B: Low risk, with a 21% chance of metastasis over five years;
- Class 2: High risk, with 72% odds of metastasis within five years.

The DecisionDx-UM test can be performed on uveal melanoma specimens obtained from either a fine needle biopsy (FNAB) performed prior to radiation therapy (plaque or proton beam), on a globe

immediately post-enucleation, or on tumor specimen obtained from an adequately preserved formalin-fixed, paraffin-embedded globe (FFPE specimen).

Per Castle Biosciences, "the GEP test can only be appropriately used when the diagnosis of primary uveal melanoma has already been established. If it is in question, measures should be taken to confirm that the tissue being provided for analysis is uveal melanoma, as this test is for prognosis only and is unable to distinguish between uveal melanoma and other tumors of the eye."

myPath® Melanoma (Myriad)

According to Myriad, the myPath® Melanoma test is intended to be used as an adjunct to histopathology when the distinction between a benign nevus and a malignant melanoma cannot be made confidently by histopathology alone.[5] The test measures the expression of 23 genes by qRT-PCR methodology and is purported to distinguish between malignant melanoma and benign nevi. An algorithm is applied that combines the measurements of gene expression, assigns a weight to each gene component, and reports a numerical score that classifies a melanocytic lesion as 'likely benign', 'likely malignant', or 'indeterminate'. The testy may be performed on a tissue block or unstained slides.

Pigmented Lesion Assay (PLA) (DermTech)

According to DermTech, the PLA is a non-invasive option to potentially identify clinically atypical pigmented lesions (or moles) at high risk for melanoma.[6] This gene expression 'signature' test that detects the expression of two specific genes, LINC00518 and PRAME, which are reported elevated in melanoma. Gene expression results are summarized in a molecular pathology report. The test uses specially designed adhesive patches to collect stratum corneum tissue rather than a surgical biopsy with a scalpel.

DecisionDx-Melanoma (Cutaneous Melanoma) (Castle Biosciences, Inc.)

According to Castle Biosciences, the DecisionDx-Melanoma test is a GEP test intended to be used to determine metastatic risk in Stage I, II, and III cutaneous melanoma patients.[7] The test is a qRT-PCR test that analyzes the expression of 31 genes associated with melanomas and uses the expression results to stratify tumors as low risk (Class 1) or high risk (Class 2). The test may be performed on formalin-fixed, paraffin embedded primary tumor tissue from either biopsy or excision.

DecisionDx DiffDx-Melanoma (Cutaneous Melanoma) (Castle Biosciences, Inc.)

According to Castle Biosciences, the DecisionDx DiffDx-Melanoma test is intended to be used in conjunction with myPath Melanoma after an intermediate result to perform gene expression profiling on 35 additional genes involved with cell differentiation and signaling. The test purports to help clinicians differentiate between a benign nevus and a malignant melanoma

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of genetic expression profile (GEP) tests as a tool for the evaluation of melanoma or suspected melanoma. Below is a summary of the available evidence identified through August 2025.

DecisionDx-UM (Uveal Melanoma)

Systematic Reviews

- In 2025, Hayes published a Molecular Test Assessment on the DecisionDX-UM test and found 7 studies in their evidence review that were deemed appropriate for review.[8] Their review found only a small number of relevant studies, and across analytical validity, clinical validity, and clinical utility, the overall quality of evidence was rated as very low. While some data suggested the test could be technically successful and show associations between risk classification and patient outcomes, significant gaps remained, including missing performance measures, limited follow-up, unclear clinical decision-making impact, and lack of strong guideline support. Hayes ultimately assigned the test a "C" rating.

- In 2017, ECRI published a genetic test product brief on the DecisionDx-UM GEP test, including six studies on clinical validity, all of which provided some clinical utility data, and one study that focused solely on utility (Plausseraud et al.).[9] This brief concluded that DecisionDx-UM can effectively identify patients with UM who are at low risk of metastasis (Class 1) from those at higher risk (Class 2) when used with standard clinical/pathologic factors, thus aiding in risk-appropriate patient management."

Clinical Utility

- In 2016, Plausseraud et al. conducted a prospective, multicenter study of 70 patients to document patient management differences and clinical outcomes associated with low-risk Class 1 (Class 1A) and high-risk Class 2 results indicated by DecisionDx-UM testing.[10] Thirty-seven patients in the prospective study were Class 1 and 33 were Class 2. Class 1 patients had 100% 3-year metastasis-free survival compared to 63% for Class 2 ($p = 0.003$) with 27.3 median follow-up months. Class 2 patients received significantly higher-intensity monitoring and more oncology/clinical trial referrals compared to Class 1 patients ($p = 2.1 \times 10^{-13}$ and $p = 0.04$, resp.). The investigators concluded that the "results of this study provide additional, prospective evidence in an independent cohort of patients that Class 1 and Class 2 patients are managed according to the differential metastatic risk indicated by DecisionDx-UM." 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.

- Clinical Application of DecisionDx-UM Gene Expression Assay Results (CLEAR) is a 5-year study designed to document the clinical application of results from DecisionDX-UM assays through physician treatment plans and to determine time to metastasis for patients with uveal melanoma. In 2020, Schefler and colleagues published results from the CLEAR II trial on 138 patients from 9 centers who were tested with the DecisionDX-UM assay.[11] Ninety-three (67%) patients were determined to have class 1 tumors by the assay, and 45 (33%) patients had class 2 tumors. Forty-two (93%) class 2 patients were referred to medical oncology specialists compared to 47 (51%)

class 1 patients ($p < 0.0001$). Physicians recommended more frequent metastatic surveillance screening for class 2 patients compared to class 1. Clas 2 patients were 4.1 times more likely to be followed with high-intensity surveillance compared to class 1 ($p < 0.001$). This study found that the DecisionDx-UM assay influenced physician treatment plans, yet it did not report on patient outcomes and no survival data was evaluated.

Cutaneous Melanoma

myPath® Melanoma (Castle Biosciences)

Systematic Reviews

In 2022, Hayes published a review of the use of myPath® Melanoma as an adjunct diagnostic tool to distinguish between benign nevi and malignant melanoma in patients with primary melanocytic lesions.[12] The review included one (industry sponsored) study for analytical validity, four clinical validity studies, and two clinical utility studies for the myPath Melanoma test. Four studies provided preliminary evidence of the clinical validity of the test reported high sensitivity and specificity of the score to aid in the diagnosis of melanocytic lesions. However, these results were derived from samples that may not represent real-world samples or indications for testing. In addition, conclusions were limited by the exclusion of indeterminate or atypical cases in some studies and the utilization of consensus histopathologic diagnoses as the standard reference in most studies. The two studies evaluating clinical utility included physician surveys and reported that the test *may* increase definitive diagnoses and impact treatment. These clinical utility studies had several limitations:

- Lack of documentation of actual treatments chosen,
- The small subsets of specific types of lesions within the study cohorts,
- Treatment changes were not solely modified by myPath Melanoma test scores, as evidenced by the lack of alignment of scores to posttest recommendations in some cases.
- Uncertainty as to the weight of the test result in the final pathology report and in treatment decisions,
- Two different groups of physicians completed the pre-test and post-test surveys (dermatopathologists for the pre-test and dermatologists for the post-test),
- Actual health outcomes were not reported.

Hayes concluded that there was insufficient evidence to support the use of the myPath Melanoma test as a diagnostic adjunctive tool to distinguish benign nevi from melanoma for indeterminate lesions. In addition, there was insufficient evidence to support the clinical use of myPath Melanoma as a guide to manage treatment decisions. Hayes graded the overall quality of evidence as very low and rated the myPath Melanoma test as a "D2".

Clinical Validity

Two studies reporting on the analytical and clinical validity of the myPath Melanoma GEP test were identified after the publication of the Hayes review above.

- In 2018, Reimann et al., compared the myPath Melanoma test with histopathology, fluorescence in situ hybridization, and SNP array for the classification of melanocytic neoplasms.[13] The myPath test

was compared to morphologic diagnosis in 198 unequivocal cases, and to morphologic diagnosis and fluorescent in situ hybridization (FISH) in 70 morphologically indeterminate cases. In the unequivocal group, FISH and myPath showed 69% inter-test agreement. In addition, the myPath assay showed 75% agreement with morphologic diagnosis, with 67% sensitivity and 81% specificity. In the indeterminate group, agreement with histopathologic interpretation was 74% for myPath. Sensitivity and specificity of FISH was 61 and 100%, respectively. However, the sensitivity and specificity of myPath was 50% and 93% for myPath, respectively. This is in contrast to the manufacturer's reported sensitivity and specificity of myPath of 90-94% and 91-96%, respectively.[5] The authors concluded that although there is good correlation between myPath and consensus diagnoses, discordant results did occur. Of note, this study was the only study identified that did not appear to be industry-sponsored. Studies reporting long-term outcomes within specific indeterminate lesion subsets are required to establish the accuracy of this test.

- In 2019, Ko et al., published an industry-sponsored retrospective analysis on 127 archived lesion samples that underwent myPath testing.[14] myPath results were compared to histopathological diagnoses and development of local recurrence, sentinel lymph node metastases, and distant metastases. Of the 65 lesions diagnosed histopathologically as melanoma, myPath results indicated that 61 of 65 (93.8%) lesions (including all lesions that metastasized) were confirmed as malignant (sensitivity). Two of the 65 (3.1%) of the histologically diagnosed lesions were determined to be benign by myPath (false negative). Of the 62 lesions diagnosed as benign by histopathology, myPath confirmed 48 of 62 (77.4%) to be benign (true negative), and 7 of 62 (11.3%) as malignant (false positive). All 14 lesions that metastasized were correctly identified by the myPath test as malignant.

- A similar 2020 industry-sponsored study by Clarke et al evaluated the accuracy of myPath in 181 melanocytic lesions.[15] Seven dermatopathologists who were blinded to gene expression test results and clinical outcomes examined the lesions to identify diagnostically uncertain cases. There were 125 cases determined to fulfill the criteria of diagnostic uncertainty. Test sensitivity for myPath in these 125 cases was 90.4% (95% CI: 79.0 -96.8%) and percent negative agreement was 95.5% (95% CI: 87.3 – 99.1%). While this study showed high sensitivity and percent negative agreement, there were a number of limitations. The sample was limited to single slides of archived melanocytic neoplasms from a previous investigation, and the investigators did not have access to complete clinical and demographic information. The retrospective design of the study prevents analysis of how the assay will influence treatment and patient-centered outcomes.

DiffDx-Melanoma

- In 2020, Estrada and colleagues published a clinical validity study assessing a diagnostic 35-gene expression profile test (DecisionDx - *DiffDx-Melanoma*) for ambiguous or difficult-to-diagnose suspicious pigmented skin lesions.[16] Diagnostic utility of 76 genes was assessed with quantitative RT-PCR; neural network modeling and cross-validation were utilized for diagnostic gene selection using 200 benign nevi and 216 melanomas for training. Validation of the 35-GEP was performed in an independent set of 273 benign and 230 malignant lesions. The test demonstrated 99.1% sensitivity, 94.3% specificity, 93.6% positive predictive value and 99.2% negative predictive value. 96.4% of cases received a differential result and 3.6% had intermediate-risk. Limitations include author conflicts of interest with the test manufacturer and a lack of evidence demonstrating clinical utility.

<u>Pigmented Lesion Assay (PLA) (DermTech)</u>

Systematic Reviews

In 2022, Hayes conducted a molecular test assessment on DermTech's PLA to help rule out melanoma without the need for a surgical biopsy of atypical lesions.[17] The evidence review included data published on osr before September 3, 2019. Eight studies were deemed appropriate for this report. Three studies were evaluated for analytical validity and demonstrated that PLA is reproducible, the assay process is optimized, and adhesive patch collection is a reliable method to collect samples, with a sample failure rate of 14%. Hayes concluded that there is moderate quality of evidence for the analytical validity of the PLA test.

From their database search, Hayes reviewers found 3 studies that were deemed appropriate to determine PLA's clinical validity (see summary of the Gerami et al study in the Clinical Validity section below). Hayes prefaces their analysis of clinical validity by explaining the importance of both sensitivity and specificity in a test to determine presence of melanoma while also emphasizing the importance of high sensitivity for this population. False negatives will delay diagnosis and treatment, potentially leading to disease progression. The 3 studies suggested that PLA has a high sensitivity and a high negative predictive value when no gene expression is detected, and dual LINC00518- and PRAME-positive lesions may be more likely to be melanoma than LINC00518- or PRAME-only positive lesions. The studies had a number of limitations: they lacked parallel comparative statistics for standard assessment and histopathology, did not clearly show that PLA improves upon primary histology reader performance, and had small sample sizes. Therefore, Hayes concluded that there is an overall low quality of evidence to support the clinical validity of the PLA test.

Hayes found 3 studies that addressed clinical utility of PLA for biopsy decision making for determining with a lesion is melanoma. Results of these studies indicated that PLA may reduce frequency of lesion biopsies for suspicion of melanoma and increase physician confidence, yet there were some limitations and obvious biases. The sample sizes were small, there was poor compliance, the studies were retrospective in design and likely suffered from selection bias, and the industry-funded studies were authored in part by employees or affiliates of the assay's manufacturer, DermTech. Hayes determined there was low-quality evidence supporting clinical utility of the PLA.

Hayes gave PLA for ruling out melanoma a C rating, stating that evidence suggests the assay can reduce the number of benign lesions biopsied and help rule out melanoma, but more long-term studies are needed to determine that PLA is noninferior or superior to current standard of expert visual assessment followed by surgical biopsy and histopathology as needed. Furthermore, more studies are needed to better understand PRAME expression optimization and the association of dual-gene-positive versus single-gene-positive PLA results and melanoma diagnosis.

Clinical Validity

- In 2017, Gerami et al., published clinical validity measures for the PLA test on a validation cohort of adults that had a clinically suspicious pigmented lesion of at least 4 mm in diameter.[18] In total, the PLA test was evaluated and validated in 555 pigmented lesions (157 training (80 melanomas and 77 non-melanomas) and 398 validation samples (87 melanomas and 311 non-melanomas)). Results were compared with standard histopathologic assessment in lesions with consensus diagnosis. In 398 validation samples (87 melanomas and 311 non-melanomas), LINC00518 and/or PRAME

expression via the PLA test appropriately differentiated melanoma from non-melanoma samples with a sensitivity of 91% and a specificity of 69%.

The study had a number of limitations, including:

- Previous testing history was not reported.
- The test was not compared to dermoscopy, which is another commonly used diagnostic tool.
- It was unclear whether the samples were all independent or multiple samples from the same patient.
- Sample selection criteria (e.g., consecutive, random) was not reported.
- The authors did not indicate if the histopathologic diagnosis was blinded to the results of the PLA.
- Dates of data collection were not reported.
- Clinical characteristics such as risk factors for melanoma and presenting symptoms were not reported.
- Short-term follow-up for the natural history of the disease.

Of note, several other industry-sponsored validation studies have been published but were not included in this evidence review for the reasons listed below:

- Gerami et al., 2014: Reported results of the development cohort and did not use the version of the test currently available on the market.[19]
- Wachsman et al., 2011: Did not use the version of the test currently marketed.[20]

The Gerami et al. clinical validity study had many methodological and reporting limitations. Therefore, the performance characteristics of the PLA test are not well characterized. In summary, additional high quality studies are needed to establish clinical validity of this test.

Clinical Utility

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without test. No direct evidence of clinical utility was identified for the PLA test.

- In 2017, Ferris and colleagues reported indirect evidence of clinical utility, assessing the potential impact of PLA on physicians' biopsy decisions in patients.[21] Forty-five dermatologists evaluated 60 clinical and dermoscopic images of atypical pigmented lesions (8 melanoma, 52 non-melanoma). In the first round, dermatologists did not have PLA test results and in the second round, dermatologists did have access to PLA 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 45x60x2=5400. Data were collected in 2014 and 2015. Results were reported for 4680 decisions with no description of the disposition of the remaining decisions. Of the 4680 reported decisions, 750 correct biopsy decisions were made without PLA results while 1331 were made with PLA results and 1590 incorrect biopsy decisions were made without PLA results while 1009 incorrect biopsy decisions were made with PLA results.

- In 2020, Brouha and colleagues investigated the effect of PLA physician decision to biopsy skin lesions clinically suspicious for melanoma.[22] The registry study found that of 3,418 pigmented skin lesions analyzed, 324 lesions (9.48%) were PLA positive and 3,094 (90.52%) were PLA negative. Among the PLA positive lesions, 316 (95.53%) were surgically biopsied. Among the PLA negative lesion, 2 (0.06%) were biopsied while the rest were monitored. This study only touches on physician influence. It does not collect data on clinical outcomes or biopsy results. Similar to the Ferris et al 2017 study, it does not offer further information on clinical utility beyond physician decision making.

<u>DecisionDx-Melanoma (Castle Biosciences)</u>

Systematic Reviews

- In 2023, ECRI gene conducted an evidence review on DecisionDX-Melanoma for evaluating prognosis and guiding management of cutaneous melanoma.[23] The review identified 8 clinical validity studies and 3 clinical utility studies published between January 2011 and March 2019. One retrospective study by Vetto et al (2019) investigated DecisionDx-Melanoma assay as a tool to predict sentinel lymph node (SLN) biopsy results. The study (n= 1421) found that patients 55 years and older with a class 1A profile had SNL positivity rates of 1.6%-4.9% and class 2B patients had SLN positivity rates of 11.9%-30.8%. [24] The study concluded that the assay identifies patients who could potentially avoid SLN biopsy. ECRI found that the study is a high risk of spectrum bias due to the high percentage of enrolled patients with T1a melanoma who underwent SLN biopsy. The participant group was therefore not representative of the typical screening population. Seven studies on clinical validity assessed the assay as a prognostic tool for rates of recurrence, metastasis, and survival. ECRI found that the majority of these studies suffered from spectrum bias, partial verification bias, and limitations due to retrospective design. Most of the studies that assesses risks of recurrence, metastasis and death reported interim data at a median follow up of 2 years or less. They concluded that data show potential for clinical value but higher-quality prospective studies with long term follow up must be conducted to enable conclusions.

  Among the 3 clinical studies, 2 were retrospective cohort studies reported on clinical management recommendation based on GEP results. One prospective cohort study by Dillon et al. compared clinical management plans before and after testing with DecisionDx-Melanoma.[25] No studies assessed the effect of using the assay on patient health outcomes such as overall survival or quality of life. ECRI concluded that the evidence for DecisionDX-Melanoma is inconclusive and more data are needed to determine effectiveness of the test.

- In 2022, Hayes published a review that evaluated the analytic validity, clinical validity and the clinical utility of the DecisionDx-Melanoma test to predict risk of metastasis and guide treatment decisions in patients with stage I or II primary cutaneous melanoma.[3] The review identified only one study reporting analytical validity, five clinical validity studies, and two clinical utility studies, all of which were industry sponsored to some degree. Hayes noted that most studies included patients not in the intended test population (stages I and II) as defined by the laboratory, although this is inaccurate as the DecisionDx-Melanoma test is designed for patients with Stage I, II, and III melanoma. Hayes also noted that the studies did not compare gene expression profile results with the standard of care staging features used in clinical practice. Two studies on clinical utility reported that test results had an impact on the management decisions of treating physicians. However, at this time, it is not clear whether DecisionDx-Melanoma adds enough prognostic information to current

clinicopathological staging factors to change patient management decisions and ultimately improve outcomes.

Hayes rated the test as a "D2"and concluded that there was insufficient evidence "to support the DecisionDx-Melanoma test's analytical validity, clinical validity, and clinical utility to predict risk of metastasis and guide treatment decisions in patients with stage I or II primary cutaneous melanoma is insufficient. Studies available do not evaluate whether the test results provide accurate, clinically actionable information resulting in improved patient outcomes."

- In 2020, Greenhaw and colleagues published an industry funded meta-analysis to determine the prognostic value of the assay by comparing clinical outcome metrics from DecisionDx-Melanoma with American Joint Committee on Cancer staging.[26] Three studies were included in the analysis, along with data from a novel cohort of 211 patients. Class 1A patients had 5-year recurrence-free rate of 91.4% and a distant metastasis-free survival rate of 94.1%. Class 2B patients had recurrence-free and metastasis-free rates of 43.6% and 55.5%, respectively. The analysis found that Class 2 was significantly associated with recurrences (hazard ratio: 2.90; $P < 0.0001$) and that considering both DecisionDx-Melanoma results and sentinel lymph node biopsy results, sensitivity and negative predictive value for distant metastasis-free survival were both improved. The study had a number of limitations. Raw data from a novel cohort was used in the analysis, yet no information was offered on the source of the data and methods of collection. The three studies included in the analysis were at high risk of bias. No studies has a randomized controlled trial design or comparator groups. One study and the raw data came from archival, retrospective data from previous studies. The studies had short median follow-up and low event rates. Study designs were dissimilar and therefore patient characteristics were likely incongruent.

- In 2020, Litchman and colleagues published a systematic review aimed to determine prognostic validity, analytic validity, and clinical utility of GEPs for primary cutaneous melanoma.[27] Twenty-nine studies were reviewed and 6 studies were included in the meta-analysis. DecisionDX-Melanoma was found to be a strong predictive test for recurrence, distant metastasis, overall survival, and sentinel lymph node biopsy positivity. The 6 studies included in the meta analysis were reviewed in both Hayes and ECRI reports and found to have high risk of bias. They are all non-comparator studies, most retrospectively conducted. A high level of heterogeneity was found between studies in terms of design, patient characteristics, and results.

Clinical Validity

In 2021, Hsueh and colleagues published results from a multi-center prospective cohort evaluating the prognostic 31-gene expression profile for cutaneous melanoma (DecsionDx-Melanoma).[28] Results from 323 patients with stage I-III cutaneous melanoma were reported at 3.2 years median follow-up. Primary end points were 3-year recurrence-free survival (RFS), distant metastasis-free survival (DMFS), and overall survival (OS). The 31-GEP was significant for RFS, DMFS, and OS in a univariate analysis and was a significant, independent predictor of RFS, DMFS, and OS in a multivariable analysis. GEP class 2 results were significantly associated with lower 3-year RFS, DMFS, and OS in all patients and those with stage I-IIA disease. Patients with stage I-IIA CM and a class 2 result had recurrence, distant metastasis, and death rates similar to patients with stage IIB-III CM. Combining 31-GEP results and AJCC staging enhanced sensitivity over each approach alone. Authors concluded that these data provide a rationale for using the 31-GEP along with AJCC staging, and suggest that patients with stage I-IIA CM and a class 2

31-GEP signature may be candidates for more intense follow-up. Limitations included the author conflicts of interest with the test manufacturer, lack of data on cause of death in some cases, and lack of long-term follow-up. As investigators noted, additional events not captured by the 3.2 year follow-up may affect recurrence rates and survival estimates.

CLINICAL PRACTICE GUIDELINES

Uveal Melanoma

National Comprehensive Cancer Network (NCCN)

In 2024, the NCCN published guidelines addressing uveal melanoma (V1.2023).[29] Authors state that "gene expression profiling (GEP) as described by Onken et al is recommended to determine whether the tumor is Class 1A (low risk), Class 1B (medium risk) or Class 2 (high risk) to inform frequency of follow-up.

Cutaneous Melanoma (CM)

National Comprehensive Cancer Network (NCCN)

In 2024, the NCCN published guidelines addressing cutaneous melanoma.[30] The guidelines recommend the use of GEP to evaluate lesions of uncertain malignancy following histology:

> "Ancillary tests to differentiate benign from malignant melanocytic neoplasms include immunohistochemistry (IHC) 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 recommend against the use of GEP in prognostic testing:

> "Despite commercially available GEP tests being marketed to risk stratify cutaneous melanoma, current GEP platforms do not provide clinically actionable prognostic information when combined or compared with known clinicopathologic factors (eg, sex, age, primary tumor location, thickness, ulceration, mitotic rate, lymphovascular invasion, microsatellites, and/or SLNB status) or multivariable nomograms/risk location, thickness, ulceration, mitotic rate, lymphovascular invasion, microsatellites, and/or SLNB status) or multivariable nomograms/risk calculators. Furthermore, the clinical utility of these tests to inform treatment recommendations and predict patient outcomes has not been established."
>
> Various studies of prognostic GEP tests suggest their role as an independent predictor of worse outcome. However, GEP is not superior to Breslow thickness, ulceration, or SLN status and it remains unclear whether available GEP tests are reliably predictive of outcome across the risk spectrum of cutaneous melanoma. Validation studies on prospectively collected, independent

cohort (similar to those performed in breast cancer) are necessary to define the clinical utility of molecular prognostic GEP testing as an adjunct to AJCC staging or as part of the multidisciplinary decision-making process to guide surveillance imaging, SLNB, and adjuvant therapy.

Existing and emerging GEP tests and other molecular techniques (ie, circulating tumor DNA tests) should be prospectively compared to determine their clinical utility, including with no-cost, contemporary, multivariable SLNB risk prediction models."[30]

American Academy of Dermatology (AAD)

In 2019, the American Academy of Dermatology (AAD) published updated guidelines on management of primary cutaneous melanoma.[31] Regarding molecular testing for CM, the guidelines state:

> "Diagnostic molecular techniques [including GEP tests] 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."

Regarding prognostic evaluation of CM, the guidelines state,

> "In the opinion of the WG [workgroup], 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".
> "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."

National Melanoma Prevention Working Group (MPWG)

In 2020, the MPWG published a non-evidence-based consensus statement assessing the clinical benefit of prognostic gene expression profiling in cutaneous melanoma.[32] Authors concluded the following:

> "More evidence is needed to support using GEP testing to inform recommendations regarding sentinel lymph node biopsy (SLNB), intensity of follow-up or imaging surveillance, and postoperative adjuvant therapy. The MPWG recommends further research to assess the validity and clinical applicability of existing and emerging GEP tests. Decisions on performing GEP testing and patient management based on these results should only be made in the context of discussion of testing limitations with the patient or within a multidisciplinary group."[32]

EVIDENCE SUMMARY

Uveal Melanoma

Although the body of evidence has some limitations, there is sufficient evidence that the DecisionDX-UM™ genetic expression profile (GEP) test can determine metastatic risk and guide surveillance and referral to specialists for follow-up. Identification of high-risk patients allows early referral to a medical oncologist and changes in management, including intensified surveillance and/or intervention, and

stratification for entry into clinical trials. In addition, current NCCN guidelines now include DecisionDX-UM risk classes in their metastatic risk algorithm in order to determine appropriate follow-up evaluation and imaging after treatment of primary disease.

There is insufficient evidence that the DecisionDX-UM™ GEP test can be useful to measure metastatic risk in patients who do not meet the criteria above in this medical policy, including but not limited to patients who do not have a confirmed diagnosis of uveal melanoma, those whose uveal cancer that has spread from another site in the body, and those whose uveal melanoma has already metastasized. Of note, the medically necessary criteria outlined above is reflective of the manufacturer's current intended use for the test.

Cutaneous Melanoma

With the exception of diagnostic testing for indeterminate melanocytic neoplasms, evidence is insufficient to support the clinical utility of gene expression assays for cutaneous melanoma. The body of evidence for each of the commercially available GEP tests for cutaneous melanoma (including myPath Melanoma, Pigmented Lesion Assay, and DecisionDx-Melanoma) requires additional clinical validity studies with prospectively collected samples and appropriate comparator tests. In addition, no direct evidence of clinical utility was identified for any commercially available GEP test. Indirect evidence of clinical utility rests on clinical validity, and since acceptable test performance for GEP tests for cutaneous melanoma has not been demonstrated, no inferences can be made about the clinical utility of these tests. Furthermore, current clinical practice guidelines, including those published by American Academy of Dermatology (AAD), do not recommend gene expression profiling for cutaneous melanomas in any circumstance. While NCCN recommends GEP testing of melanocytic neoplasms of uncertain biologic potential, both NCCN and the AAD consider GEP tests to be emerging and still require studies that demonstrate clinical utility.

HEALTH EQUITY CONSIDERATIONS

The Centers for Disease Control and Prevention (CDC) defines health equity as the state in which everyone has a fair and just opportunity to attain their highest level of health. Achieving health equity requires addressing health disparities and social determinants of health. A health disparity is the occurrence of diseases at greater levels among certain population groups more than among others. Health disparities are linked to social determinants of health which are non-medical factors that influence health outcomes such as the conditions in which people are born, grow, work, live, age, and the wider set of forces and systems shaping the conditions of daily life. Social determinants of health include unequal access to health care, lack of education, poverty, stigma, and racism.

The U.S. Department of Health and Human Services Office of Minority Health calls out unique areas where health disparities are noted based on race and ethnicity. Providence Health Plan (PHP) regularly reviews these areas of opportunity to see if any changes can be made to our medical or pharmacy policies to support our members obtaining their highest level of health. Upon review, PHP creates a Coverage Recommendation (CORE) form detailing which groups are impacted by the disparity, the research surrounding the disparity, and recommendations from professional organizations. PHP Health Equity COREs are updated regularly and can be found online here.

BILLING GUIDELINES AND CODING

CODES*		
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 (FFPE) tissue, algorithm reported as a categorical result (ie, benign, indeterminate, 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 (i.e., benign, intermediate, malignant)
	0578U	Oncology (cutaneous melanoma), RNA, gene expression profiling by realtime 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
	81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
	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
HCPCS	None	

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for

Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

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POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.

12/2023	Annual update. Change policy title. Added criterion regarding repeat testing.
11/2024	Annual update. Added criterion III. Added prior authorization to two codes.
10/2025	Annual update and Q4 code set update. . Added changes to documentation requirements.