

<b>MEDICAL POLICY</b>	<b>Genetic Testing: Genetic Expression Profile Testing for Melanoma (All Lines of Business Except Medicare)</b>	
<b>Effective Date: 1/1/2021</b>   <div style="text-align: right;">1/1/2021</div>	Section: GT	Policy No: 442
	Medical Policy Committee Approved Date: 7/19; 11/19; 9/2020; 12/2020	
Medical Officer	Date	

See Policy CPT CODE section below for any prior authorization requirements

**SCOPE:**

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

**APPLIES TO:**

All lines of business except Medicare

**BENEFIT APPLICATION**

Medicaid 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.

**POLICY CRITERIA**

Uveal Melanoma

- I. The DecisionDx-UM™ gene expression profile (GEP) test may be considered **medically necessary and covered** in patients with a confirmed diagnosis of primary, localized uveal melanoma with no evidence of metastasis.
- II. GEP test(s) for uveal melanoma are considered **investigational and not covered** for patients that do not meet the above criterion I., including but not limited to:
  - 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.

<b>MEDICAL POLICY</b>	<b>Genetic Testing: Genetic Expression Profile Testing for Melanoma (All Lines of Business Except Medicare)</b>
-----------------------	---

<p>C. Patients whose uveal melanoma has already metastasized.</p> <p>D. Use of GEP test other than DecisionDx-UM™.</p> <p><u>Cutaneous Melanoma</u></p> <p>III. Gene expression profile tests for cutaneous melanoma are considered <b>investigational and not covered in all situations</b>, including but not limited to:</p> <p>A. To guide initial biopsy decisions (e.g., Pigmented Lesion Assay [PLA]).</p> <p>B. To evaluate or aid in the diagnosis of atypical/indeterminate lesions (e.g., myPath Melanoma).</p> <p>C. To determine metastatic risk (e.g., DecisionDx-Melanoma).</p> <p>Link to <a href="#">Policy Summary</a></p>
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**CPT CODES**

All Lines of Business Except Medicare	
Prior Authorization Required	
0081U	TERMED 12/31/19 <del>Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping genes), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis</del>
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)
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
Not Covered	
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, malignant)
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

<b>MEDICAL POLICY</b>	<b>Genetic Testing: Genetic Expression Profile Testing for Melanoma (All Lines of Business Except Medicare)</b>
-----------------------	---

<p><b>Unlisted Codes</b>  All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then <b>prior-authorization is required.</b></p>	
81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis
84999	Unlisted chemistry procedure

**DESCRIPTION**

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.<sup>1</sup>

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.<sup>1</sup>

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.<sup>1</sup> 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.<sup>2</sup>

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

<b>MEDICAL POLICY</b>	<b>Genetic Testing: Genetic Expression Profile Testing for Melanoma (All Lines of Business Except Medicare)</b>
-----------------------	---

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.<sup>3</sup> 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).<sup>4</sup> 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.<sup>5</sup> 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 test may be performed on a tissue block or unstained slides.

<b>MEDICAL POLICY</b>	<b>Genetic Testing: Genetic Expression Profile Testing for Melanoma (All Lines of Business Except Medicare)</b>
-----------------------	---

*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.<sup>6</sup> 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.<sup>7</sup> 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.

**REVIEW OF EVIDENCE**

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 June of 2020.

**DecisionDx-UM (Uveal Melanoma)**

Systematic Reviews

In June 2016, Hayes published a review of the DecisionDx-UM test, including only 3 studies for analytic validity, 4 clinical validity studies, and 1 clinical utility study.<sup>8</sup> At this time Hayes gave the test a “D2” as a “prognostic indicator of distant metastasis within five years in patients with uveal melanoma. This rating is based on the very-low-quality evidence for analytic validity, very-low-quality evidence for clinical validity, and insufficient evidence to evaluate the impact on health outcomes.” However, this initial review also indicated that in 2016 there were no clinical practice guidelines addressing this test, nor were any payers allowing for coverage.

In June 2020, Hayes published a Molecular Test Assessment on the DecisionDX-UM test and found 3 studies in their evidence review that were deemed appropriate for review.<sup>9</sup> One study by Plasseraud and colleagues addressed analytical validity and found a 5-year technical assessment rate of 96% for the assay.<sup>10</sup> The study failed to include parameters such as sensitivity, linearity, or amplification efficiency, and did not address the intratumor heterogeneity of the samples, and was considered a very low body of evidence by Hayes. For clinical validity, 7 studies were identified and one study by Demirci and colleagues was included for analysis.<sup>11</sup> The retrospective clinical data analysis included 293 patients and

<b>MEDICAL POLICY</b>	<b>Genetic Testing: Genetic Expression Profile Testing for Melanoma (All Lines of Business Except Medicare)</b>
-----------------------	---

found that DecisionDx-UM risk class association was associated with 3-year metastasis-free survival. The study’s limitations included a short follow up and retrospective design. One study by Plasseraud and colleagues was identified that assessed clinical utility.<sup>12</sup> An interim analysis was conducted on the prospective CLEAR trial, which tracks clinical application of DecisionDX-UM assay results and associated patient outcomes. The results found an association between clinical management decisions and DecisionDx-UM risk classes, although physician decisions were not clear. Hayes reported that there was a very low quality body of evidence supporting clinical utility of the test.

Hayes concluded, “There is insufficient evidence to support the use of the DecisionDx-UM test to identify the likelihood of metastasis within 5 years in patients with UM. Although an established assay process is in place, the validity of the test and the impact on patient management is unclear; additional data are needed to support the use of this test.”<sup>9</sup>

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.).<sup>13</sup> This brief concluded:

“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 Validity: Key Studies

In 2012, Onken et al. published the results of a large, prospective, multiinstitutional study reporting on clinical validation of the DecisionDx-UM assay in 459 patients with primary melanoma.<sup>14</sup> This study is referenced in the NCCN guidelines, where the classes determined by the GEP test are listed as prognostic factors in the guideline. Median follow-up of this was 17.4 months (mean, 18.0 months). Metastasis was detected in 3 (1.1%) class 1 cases and 44 (25.9%) class 2 cases ( $P < 10^{-14}$ ). The GEP demonstrated superior prognostic accuracy over the presence of monosomy of chromosome 3 ( $P = 0.0001$ ). Using multivariate analysis, GEP class had a stronger independent association with metastasis than any other prognostic factor ( $P < 0.0001$ ). 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.

Additional clinical validity studies with similarly large sample sizes (n=299, 399, 609) have been reported previously and included in the reviews, and will not be summarized here. Collectively, the large clinical validity studies have rates of metastasis of patients with a Class 1 GEP result ranged from 1.1% - 6%, while the rates for those categorized as Class 2 ranged from 25.9% to 39.6%.

Clinical Utility

In 2014, Aaberg et al. addressed the impact of using the 15 GEP results on treatment decisions in a study in which ocular oncologists were queried regarding their use of the test to guide treatment decisions.<sup>15</sup> One component of this study was to review the medical records on 191 patients on whom GEP was

<b>MEDICAL POLICY</b>	<b>Genetic Testing: Genetic Expression Profile Testing for Melanoma (All Lines of Business Except Medicare)</b>
-----------------------	---

performed. In this group, 58% had a class 1 signature and 42% had a class 2 signature. Of these patients, 88 (46%) had detailed treatment plans in their records (total, n=88; 48 class 1 and 40 class 2 patients). All class 1 patients received a low-intensity surveillance plan, whereas all class 2 patients received a high-intensity surveillance plan (including more frequent liver function tests and more frequent liver imaging and/or systemic evaluations). In addition, 36 patients had information regarding referrals; all class 2 (n=23) were referred to medical oncology and none of the class 1 patients (n=13) were referred (P<0.0001). Ultimately, the authors had no health outcome data but suggested that outcomes in class 2 patients might be improved by using more intensive surveillance.

The second component of this study was based on a 2012 survey of the treating physicians. Of the 54 physicians surveyed, 29 (74%) changed metastasis surveillance based on GEP and cytogenetic information, 8 (21%) did not use GEP results to manage patients, 2 (5%) referred patients to medical oncology, 6 (15%) recommended prophylactic therapy, and 9 (23%) referred patients to a clinical trial or initiated investigational therapy.

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.<sup>12</sup> 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, Scheffler and colleagues published results from the CLEAR II trial on 138 patients from 9 centers who were tested with the DecisionDX-UM assay.<sup>16</sup> 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. Class 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.

<b>MEDICAL POLICY</b>	<b>Genetic Testing: Genetic Expression Profile Testing for Melanoma (All Lines of Business Except Medicare)</b>
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**Cutaneous Melanoma**

myPath® Melanoma (Myriad)

*Systematic Reviews*

In 2018 (reviewed in 2020), 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.<sup>17</sup> 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.<sup>18</sup> 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

<b>MEDICAL POLICY</b>	<b>Genetic Testing: Genetic Expression Profile Testing for Melanoma (All Lines of Business Except Medicare)</b>
-----------------------	---

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.<sup>5</sup> 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.<sup>19</sup> 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.<sup>20</sup> 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.

The performance characteristics of the myPath Melanoma test are not well characterized. In summary, additional high quality studies are needed to establish clinical validity of this test.

Pigmented Lesion Assay (PLA) (DermTech)

*Systematic Reviews*

In 2019 (reviewed in 2020), 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.<sup>21</sup> The evidence review included data published on or before September 3, 2019. Eight studies were deemed appropriate for this report. Three studies were evaluated for analytical validity and demonstrated that PLA is

<b>MEDICAL POLICY</b>	<b>Genetic Testing: Genetic Expression Profile Testing for Melanoma (All Lines of Business Except Medicare)</b>
-----------------------	---

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.<sup>22</sup> 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.

<b>MEDICAL POLICY</b>	<b>Genetic Testing: Genetic Expression Profile Testing for Melanoma (All Lines of Business Except Medicare)</b>
-----------------------	---

- 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.<sup>23</sup>
- Wachsman et al., 2011: Did not use the version of the test currently marketed.<sup>24</sup>

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.

However, one study by Ferris et al. in 2017 was identified that reported indirect evidence of clinical utility. This study assessed the potential impact of PLA on physicians' biopsy decisions in patients.<sup>25</sup> 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.

A 2020 industry-funded study by Brouha and colleagues investigated the effect of PLA physician decision to biopsy skin lesions clinically suspicious for melanoma.<sup>26</sup> 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

<b>MEDICAL POLICY</b>	<b>Genetic Testing: Genetic Expression Profile Testing for Melanoma (All Lines of Business Except Medicare)</b>
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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.

DecisionDx-Melanoma (Castle Biosciences)

*Systematic Reviews*

- In 2019, ECRIgene conducted an evidence review on DecisionDX-Melanoma for evaluating prognosis and guiding management of cutaneous melanoma.<sup>28</sup> 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%.<sup>29</sup> 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.<sup>30</sup> 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 2018, 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.<sup>3</sup> 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

<b>MEDICAL POLICY</b>	<b>Genetic Testing: Genetic Expression Profile Testing for Melanoma (All Lines of Business Except Medicare)</b>
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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.”

Two systematic reviews were published in 2020 on DecisionDX-Melanoma as a prognostic test for primary cutaneous melanoma. 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.<sup>31</sup> 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.

The second systematic review by Litchman and colleagues aimed to determine prognostic validity, analytic validity, and clinical utility of GEPs for primary cutaneous melanoma.<sup>32</sup> 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.

Overall, the 2020 systematic reviews found that DecisionDx-Melanoma may have predictive value in cutaneous melanoma prognosis based on low level studies, yet they did not address the effect the assay has on treatment plans and patient-centered outcomes such as quality of life or overall survival.

<b>MEDICAL POLICY</b>	<b>Genetic Testing: Genetic Expression Profile Testing for Melanoma (All Lines of Business Except Medicare)</b>
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## **CLINICAL PRACTICE GUIDELINES**

### Uveal Melanoma

#### *National Comprehensive Cancer Network (NCCN)*

Current (V 1.2020, published May 21, 2020) NCCN guidelines for uveal melanoma state in the recommendations for initial work-up and staging to “consider biopsy for prognostic analysis for risk stratification”.<sup>33</sup>

The guidelines further states in the footnotes that the “specimen should be sent for cytology, chromosome analysis, *and/or* gene expression profiling.”

In addition, follow-up after primary treatment includes an algorithm to determine risk of distant metastases (page UM-4, highlighted in yellow) that specifically includes the class determined by the DecisionDx-UM assay in each category of risk. NCCN cites a pivotal prospective validation study (Onken et al., 2012)<sup>14</sup>, as the basis for this recommendation. See summary of the Onken study in the evidence section above.

### Cutaneous Melanoma (CM)

#### *National Comprehensive Cancer Network (NCCN)*

The 3.2020 NCCN guideline for cutaneous melanoma mentions gene expression profile tests in the context of initial evaluation of suspicious lesions and work-up after clinical staging.<sup>34</sup> In the recommendations section of the guideline, the panel states the following:

“Prognostic gene expression profiling (GEP) to differentiate melanomas at low versus high risk for metastasis may provide information on individual risk of recurrence, as an adjunct to standard AJCC staging. However, the currently available prognostic molecular techniques should not replace pathologic staging procedures, and the use of GEP testing according to specific melanoma stage (before or after SLNB) requires further prospective investigation in larger, contemporary data sets of unselected patients.”

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

<b>MEDICAL POLICY</b>	<b>Genetic Testing: Genetic Expression Profile Testing for Melanoma (All Lines of Business Except Medicare)</b>
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Regarding prognostic testing, NCCN indicates that “it is unclear whether these tests provide clinically actionable prognostic information. Furthermore, the impact of these tests on treatment outcomes or follow-up schedules has not been established.”

Additionally, with regards to diagnostic testing for indeterminate melanocytic neoplasms following histology, the panel states that ancillary methods to detect genetic alterations in these lesions may include gene expression profiling. However, “although they may provide complementary information to inform a better understanding of the biologic nature of melanocytic neoplasms, these tests cannot replace the gold standard of diagnostic histopathologic examination by an expert dermatologist. Their utility is still under evaluation and more data are needed before they can be routinely recommended.”

*American Academy of Dermatology (AAD)*

In 2019, the American Academy of Dermatology (AAD) published updated guidelines on management of primary cutaneous melanoma.<sup>35</sup> 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 Institute for Health and Care Excellence (NICE)*

In 2015, the National Institute for Health and Care Excellence (NICE) published guidelines on the assessment and management of melanoma.<sup>36</sup> They recommended against genetic testing for early-stage melanoma, stating: “Do not offer genetic testing of stage IA–IIB primary melanoma at presentation except as part of a clinical trial.”

They do recommend considering genetic testing for later stage melanoma, stating: “Consider genetic testing of stage IIC primary melanoma or the nodal deposits or in-transit metastases for people with stage III melanoma... If insufficient tissue is available from nodal deposits or in-transit metastases, consider genetic testing of the primary tumour for people with stage III melanoma.”

<b>MEDICAL POLICY</b>	<b>Genetic Testing: Genetic Expression Profile Testing for Melanoma (All Lines of Business Except Medicare)</b>
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## **POLICY 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

There is insufficient published evidence to make reliable conclusions regarding the clinical validity and 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) require 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 the National Comprehensive Cancer Network (NCCN) and American Academy of Dermatology (AAD), do not recommend gene expression profiling for cutaneous melanomas in any circumstance. Both NCCN and the AAD consider GEP tests to be emerging and still require studies that demonstrate clinical utility.

## **INSTRUCTIONS FOR USE**

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature.

<b>MEDICAL POLICY</b>	<b>Genetic Testing: Genetic Expression Profile Testing for Melanoma (All Lines of Business Except Medicare)</b>
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The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

**REGULATORY STATUS**

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

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**MEDICAL POLICY****Genetic Testing: Genetic Expression Profile Testing for Melanoma (All Lines of Business Except Medicare)**

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**MEDICAL POLICY****Genetic Testing: Genetic Expression Profile Testing for Melanoma (All Lines of Business Except Medicare)**

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<b>MEDICAL POLICY</b>	<b>Genetic Testing: Genetic Expression Profile Testing for Melanoma (All Lines of Business Except Medicare)</b>
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