MEDICAL POLICY

POLICY TITLE	GENE EXPRESSION PROFILING FOR MELANOMA
POLICY NUMBER	MP 2.360

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**1/1/2025**

I. POLICY

Gene Expression Profiling for Uveal Melanoma

Gene expression profiling for uveal melanoma with DecisionDx-UM is **medically necessary** for patients with primary, localized uveal melanoma.

Gene expression profiling for uveal melanoma that do not meet the above criteria is **investigational.** There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Gene Expression Profiling for Cutaneous Melanoma

Gene expression testing, including but not limited to the Pigmented Lesion Assay, in the evaluation of patients with suspicious pigmented lesions is considered **investigational**.

Gene expression testing, including but not limited to the myPath Melanoma test, in the evaluation of patients with melanocytic lesions with indeterminate histopathologic features is considered **investigational**.

Gene expression testing, including but not limited to DecisionDx-Melanoma, in the evaluation of patients with cutaneous melanoma is considered **investigational** for all indications. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with these procedures.

Policy Guidelines

Genetic Counseling
Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals

understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Cross-reference:

MP 2.246 Genetic Testing for Familial Cutaneous Malignant Melanoma
MP 2.277 Miscellaneous Genetic and Molecular Diagnostic Tests

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

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Uveal Melanoma

The uveal tract is the middle layer of the wall of the eye; it has three main parts: the choroid (a tissue layer filled with blood vessels), ciliary body (muscle tissue that changes the shape of the pupil and the lens), and the iris (the colored part of the eye). Uveal melanoma arises from melanocytes in the stroma of the uveal tract. Approximately 90% of uveal melanomas arise in the choroid, 7% in the ciliary body, and 3% in the iris.

Uveal melanoma, although rare, is the most common primary intraocular malignancy in adults. Mean age-adjusted incidence of uveal melanoma in the United States is 6.3 per million people among whites, 0.9 among Hispanics, and 0.24 among Black people. Uveal melanoma has a progressively rising, age-specific, incidence rate that peaks near age 70. Host susceptibility factors associated with the development of this cancer include white race, fair skin, and light eye color.

Treatment

Treatment of primary, localized uveal melanoma can be by surgery or radiotherapy. In general, larger tumors require enucleation surgery and smaller tumors can be treated with radiotherapy, but specific treatment parameters are lacking. The most common treatment of localized uveal melanoma is radiotherapy, which is preferred because it can spare vision in most cases. For smaller lesions, randomized controlled trials (RCTs) have shown that patients receiving radiotherapy or enucleation progress to metastatic disease at similar rates after treatment. Radiotherapy can be delivered by various mechanisms, most commonly brachytherapy and proton beam therapy. Treatment of primary uveal melanoma improves local control and spares

vision; however, the 5-year survival rate (81.6%) has not changed over the last 3 decades, suggesting that life expectancy is independent of successful local eye treatment.

Uveal melanomas disseminate hematogenously and metastasize primarily to the liver and lungs. Treatment of hepatic metastases is associated with prolonged survival and palliation in some patients. Therapies directed at locoregional treatment of hepatic metastases include surgical and ablative techniques, embolization, and local chemotherapy.

Metastatic Disease
It is unusual for patients with uveal melanoma to have distant metastases at presentation, with less than 1% presenting with metastases when they are treated for their intraocular disease; but they are at risk for distant metastases, particularly to the liver, for years after presentation. The prospective, longitudinal Collaborative Ocular Melanoma Study (2005) followed 2320 patients with choroidal melanoma with no melanoma metastasis at baseline who were enrolled in randomized controlled trials to evaluate forms of radiotherapy for choroidal melanoma for 5 to 10 years. During follow-up, 739 patients were diagnosed with at least 1 site of metastasis, of which 660 (89%) were liver. Kaplan-Meier estimates of 2-, 5-, and 10-year metastasis rates were 10% (95% confidence interval, 9% to 12%), 25% (95% confidence interval, 23% to 27%), and 34% (95% confidence interval, 32% to 37%), respectively.

Prognosis
Metastatic disease is the leading cause of death in patients with uveal melanoma, and approximately 50% of patients will develop distant metastasis. A number of factors may be used to determine prognosis, but the optimal approach is uncertain. The most important clinical factors that predict metastatic disease are tumor size (measured in diameter or thickness), ciliary body involvement, and transscleral extension. Clinical staging using the American Joint Committee on Cancer recommendations allows risk stratification for metastatic disease. In a retrospective study of 3377 patients with uveal melanoma (2015), in which staging was performed using American Joint Committee on Cancer classifications, the rate of metastasis-free survival at 5 years was 97% for stage I, 89% for stage IIA, 79% for stage IIB, 67% for stage IIIA, 50% for stage IIIB, and 25% for stage IIIB.

Genetic Analysis
Genetic analysis of uveal melanoma can provide prognostic information for the risk of developing metastatic disease. Prescher et al (1996) showed that monosomy of chromosome three correlated strongly with metastatic death, with a 5-year survival reduction from 100% to 50%. Subsequent studies have reported that, based on genetic analysis, there were two distinct types of uveal melanomas—those with monosomy chromosome three associated with a very poor prognosis and those with disomy 3 and 6p gain associated with a better prognosis. The *BAP1* gene has been identified as an important marker of disease type. In one study (2016), 89% of tumors with monosomy three had a *BAP1* variant, and no tumors without monosomy three had a *BAP1* variant.

Gene expression profiling determines the expression of multiple genes in a tumor and has been proposed as an additional method to stratify patients into prognostic risk groups.

REGULATORY STATUS
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). The DecisionDx-UM® test (Castle Biosciences, Phoenix, AZ) is available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

Cutaneous Melanoma
Cutaneous melanoma accounts for more than 90% of cases of melanoma. For many decades, melanoma incidence was rapidly increasing in the United States. However, recent estimates have suggested the rise may be slowing. In 2018, more than 90,000 new cases of melanoma are expected to be diagnosed, and more than nine thousand people are expected to die of melanoma.

Risk Factors
Exposure to solar ultraviolet radiation is a major risk factor for melanoma. Most melanomas occur on the sun-exposed skin, particularly those areas most susceptible to sunburn. Likewise, features that are associated with an individual's sensitivity to sunlight, such as light skin pigmentation, red or blond hair, blue or green eyes, freckling tendency, and poor tanning ability are well-known risk factors for melanoma. There is also a strong association between high total body nevus counts and melanoma.

Several genes appear to contribute to melanoma predisposition such as tumor suppressor gene *CDKN2A*, melanocortin-1 receptor (*MC1R*) gene, and *BAP1* variants. Individuals with either familial or sporadic melanoma have a 2 to 3 times increased risk of developing a subsequent primary melanoma. Several occupational exposures and lifestyle factors, such as body mass index and smoking, have been evaluated as possible risk factors for melanoma.

Gene Expression Profiling
Gene expression profiling (GEP) measures the activity of thousands of genes simultaneously and creates a snapshot of cellular function. Data for GEP are generated by several molecular technologies including DNA microarrays that measures activity relative to previously identified genes and RNA-Seq that directly sequences and quantifies RNA molecules. Clinical applications of GEP include disease diagnosis, disease classification, prediction of drug response, and prognosis.

REGULATORY STATUS
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. The Pigmented Lesion Assay, myPath Melanoma, and DecisionDx-Melanoma tests are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed

by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

IV. RATIONALE

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Uveal Melanoma

SUMMARY OF EVIDENCE

For individuals who have localized uveal melanoma who receive a GEP test for uveal melanoma (DecisionDx-UM), the evidence includes cross-sectional studies of assay validation and clinical validity. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, other test performance measures, functional outcomes, health status measures, and quality of life. One commercially available test identified (DecisionDx-UM) has published data related to its clinical validity and is the focus of this review. Six studies of clinical validity identified used the GEP score to predict melanoma metastases and melanoma-specific survival. All six reported that GEP classification correlated strongly with metastatic disease and melanoma mortality. Four studies compared GEP classification with other prognostic markers, and GEP class had the strongest association among the markers tested. GEP classification appears to be a strong predictor of metastatic disease and melanoma death. There are no studies directly showing clinical utility. Absent direct evidence, a chain of evidence can be constructed to determine whether using the results of GEP testing for management decisions improves the net health outcome of patients with uveal melanoma. Aaberg et al (2014) have shown an association between GEP classification and treatment, reporting that patients classified as low risk were managed with less frequent and intensive surveillance and were not referred for adjuvant therapy. It is uncertain whether stratification of patients into higher risk categories has the potential to improve outcomes by allowing patients to receive adjuvant therapies through detection of metastases earlier. However, classification into the low-risk group would support a reduction in the burden of surveillance without apparent harm. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Cutaneous Melanoma

SUMMARY OF EVIDENCE

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

For individuals who have melanocytic lesions with indeterminate histopathologic features who receive GEP with the myPath Melanoma test added to histopathology to aid in the diagnosis of melanoma, the evidence includes observational studies. Relevant outcomes are overall survival, disease-specific survival, test validity, change in disease status, and treatment-related morbidity. The myPath test has two clinical validity studies including long-term follow-up for metastasis as the reference standard. In one study, it is not clear whether the study population included lesions that were indeterminate following histopathology. The second study focused on indeterminate lesions but had limitations including a retrospective design and less than 5-year follow-up in 31% of cases. Therefore, performance characteristics are not well-characterized. No direct evidence of clinical utility was identified. Given that the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility through a chain of evidence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with American Joint Committee on Cancer (AJCC) stage I to III cutaneous melanoma who receive GEP with the DecisionDx-Melanoma test to inform management decisions regarding surveillance, the evidence includes retrospective and perspective observational studies. Relevant outcomes are overall survival, disease-specific survival, test validity, change in disease status, resource utilization and treatment-related morbidity. The DecisionDx-Melanoma test has three independent clinical validity studies that have reported five -year recurrence-free survival (RFS) in AJCC stage I or II patients. Gerami et al (2015) reported RFS rates of 37 % in DecisionDx class 2 (high-risk) in patients in AJCC stage I and II patients combined. Zager et al (2018) reported RFS rates of 85% (95% confidence interval, 74% to 97%) for DecisionDx class 2 patients with AJCC stage I and 55% (95% confidence interval, 44% to 69%) for DecisionDx class 2 in AJCC stage II disease. RFS does not appear to be well characterized as evidenced by the variation in estimates across studies. This indication is to 'rule-in' patients for enhanced surveillance; therefore, specificity and positive predictive value (PPV) are key performance characteristics. Zager et al (2018) and Greenhaw et al (2018) the specificities were 71% and 87% respectively while the PPV were 48% and 24%, respectively. The PPV suggests that the majority of patients identified as high-risk by the DecisionDx test would not develop metastasis and would be unnecessarily subjected to additional surveillance. Greenhaw et al (2018) also reported that in 219 AJCC stage I patients, 201 had DecisionDx class 1 (low risk) scores and 18 had DecisionDx class 2 (high-risk) scores. The only metastasis in stage I patients occurred in a patient with a DecisionDx class 1 score. Therefore, none of their stage 1 patients benefited from DecisionDx testing but 18 (8%) were incorrectly identified as high-risk for metastasis and could have received unnecessary surveillance. Five-year RFS data are not available for the subgroup of patients for whom a 'rule-out' test would be relevant (class IIB through III). There is no evidence that changes to the frequency and methods for surveillance improve outcomes. Given that, the evidence is insufficient to demonstrate test performance and there is no evidence that changes in surveillance improve outcomes, no inferences can be made about clinical utility through a chain of evidence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with AJCC stage I or II cutaneous melanoma who receive GEP with the DecisionDx-Melanoma test to inform management decisions regarding adjuvant therapy, the

evidence includes retrospective and prospective observational studies. Relevant outcomes are overall survival, disease-specific survival, test validity, change in disease status, resource utilization and treatment-related morbidity. The DecisionDx-Melanoma test has three independent clinical validity studies that have reported 5-year RFS in AJCC stage I or II patients. Gerami et al (2015) reported RFS rates of 37% for DecisionDx class 2 (high-risk) in patients in AJCC stage I and II patients combined. Zager et al (2018) reported RFS rates of 85% (95% confidence interval, 74% to 97%) for DecisionDx class 2 patients in AJCC stage 1 and 55% (95% confidence interval, 44% to 69%) for DecisionDx class 2 in AJCC stage II disease. RFS does not appear to be well-characterized as evidenced by the variation in estimates across studies. This indication is to 'rule-in' patients for adjuvant therapy; therefore, specificity and PPV are key performance characteristics. In Zager et al (2018) and Greenhaw et al (2018) the specificities were 71% and 87% respectively while the PPV were 48% and 24%, respectively. The PPV suggests that the majority of patients identified as high-risk by the DecisionDx test would not develop metastasis and would be unnecessarily subjected to additional treatment. Greenhaw et al (2018) also reported that in 219 AJCC stage I patients, 201 had DecisionDx class 1 (low risk) scores and 18 had DecisionDx class 2 (high-risk) scores. The only metastasis in stage I patients occurred in a patient with a DecisionDx class 1 score. Therefore, none of their stage 1 patients benefited from DecisionDx testing but 18 (8%) were incorrectly identified as high-risk for metastasis and could have received unnecessary treatment. There is no evidence that adjuvant therapy improves outcomes in these patients. Given that the evidence is insufficient to demonstrate test performance and there is no evidence that adjuvant therapy improves outcomes, no inferences can be made about clinical utility through a chain of evidence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with stage, I or II cutaneous melanoma with clinically negative sentinel node basins who are being considered for sentinel lymph node (SLN) biopsy who receive GEP with the DecisionDx-Melanoma test to determine whether to perform SLN biopsy, the evidence includes retrospective observational studies. Relevant outcomes are overall survival, disease-specific survival, test validity, change in disease status, resource utilization and treatment-related morbidity. The DecisionDx-Melanoma test has three independent clinical validity studies that have reported 5-year RFS in AJCC stage I or II patients. Gerami et al (2015) reported RFS rates of 98% in DecisionDx class 1 (low risk) without confidence intervals, in AJCC stage I or II patients. Zager et al (2017) reported RFS rates of 96% (95% confidence interval, 94% to 99%) for DecisionDx class 1 in patients with AJCC stage I disease; they also reported RFS rates of 74% (95% confidence interval, 60% to 91%) for DecisionDx class 1 in patients with AJCC stage II disease. Although confidence intervals were not available for the first study, RFS does not appear to be well-characterized as evidenced by the variation in estimates across studies. Zager et al (2017) also reported that in fifty-six patients who were DecisionDx class 1 (low-risk) but SLN biopay-positive, twenty-two recurrences (39%) occurred over 5 years. If the DecisionDx test were used as a triage for SLN biopsy, these patients would not undergo SLN biopsy and would likely not receive adjuvant therapy, which has shown to be effective at prolonging time to recurrence in node-positive patients. Data on 5-year RFS is not available for the target population (Class 1A patients ≤55 years old who have tumors less than 2 mm deep [T1-T2]) outside of the retrospective cohort that was used to identify the target population. No direct

evidence of clinical utility was identified. Given that the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility through a chain of evidence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

V. DEFINITIONS

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NA

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. Member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross' medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary for UVEAL melanoma:

Procedure Codes							
81552							

ICD-10-CM Diagnosis Code	Description
C69.30	Malignant neoplasm of unspecified choroid
C69.31	Malignant neoplasm of right choroid
C69.32	Malignant neoplasm of left choroid
C69.40	Malignant neoplasm of unspecified ciliary body
C69.41	Malignant neoplasm of right ciliary body
C69.42	Malignant neoplasm of left ciliary body

Investigational, therefore not covered for CUTANEOUS melanoma:

Procedure Codes							
0089U	0090U	0314U	0490U	81529			

IX. REFERENCES

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70. Blue Cross Blue Shield Association Medical Policy Reference Manual. 2.04.146 Gene Expression Profiling for Cutaneous Melanoma. June 2023

X. POLICY HISTORY

TOP

MP 2.360	**05/30/2018 New Policy**. Adopting BCBSA. Gene expression profiling for uveal melanoma with DecisionDx-UM is **medically necessary** for patients with primary, localized uveal melanoma. Gene expression profiling for cutaneous melanoma is **investigational**. Coding added.
	01/04/2019 Administrative Update. Added new code for DecisionDx-UM 0081U effective 1/1/2019. Removed unspecified codes from medically necessary coding section.
	03/21/2019 Consensus Review. No changes made to policy statement. Updated references.
	07/01/2019 Administrative Update. Added new code for Pigmented Lesion Assay (PLA)/DermTech 0089U and myPath 0090U as investigational for cutaneous melanoma
	01/01/2020 Administrative Update. Added new code 81552. Removed end-dated code 0081U.
	03/04/2020 Consensus Review. Policy updated with literature. Policy statements unchanged.
	01/01/2021 Administrative Update. Added new code 81529; effective 1/1/21.
	05/26/2021 Consensus Review. No change to policy statement. Background, Rationale and References updated.
	03/11/2022 Administrative Update. New code 0314U added; effective 4/1/2022
	09/09/2022 Consensus Review. Policy statement unchanged. NCCN language added. FEP language revised. Background, Rationale and References updated.
	12/01/2022 Administrative Update. New Code 0357U added; effective 1/1/23
	07/03/2023 Consensus Review. Policy statements unchanged. References updated. Coding reviewed. Removed 0357U as it is a deleted code.

POLICY TITLE	GENE EXPRESSION PROFILING FOR MELANOMA
POLICY NUMBER	MP 2.360

	02/05/2024 Consensus Review. Policy statement unchanged. References updated. Coding reviewed. Codes 81599, 84999, and 81479 removed.
	09/18/2024 Administrative Update. New code 0490U added; effective 10/1/2024.
	11/20/2024 Administrative Update. Removed NCCN statement.

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