

MEDICAL POLICY

POLICY TITLE	GENE EXPRESSION PROFILING FOR UVEAL MELANOMA
POLICY NUMBER	MP 2.360

CLINICAL BENEFIT	<input type="checkbox"/> MINIMIZE SAFETY RISK OR CONCERN. <input checked="" type="checkbox"/> MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. <input type="checkbox"/> ASSURE APPROPRIATE LEVEL OF CARE. <input type="checkbox"/> ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. <input checked="" type="checkbox"/> ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. <input type="checkbox"/> ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	RETIRED 7/1/2026

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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.

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 2.277 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.

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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

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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.

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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.

V. DEFINITIONS

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NA

VI. DISCLAIMER

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Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

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VII. 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
C69.80	Malignant neoplasm of overlapping sites of unspecified eye and adnexa
C69.81	Malignant neoplasm of overlapping sites of right eye and adnexa
C69.82	Malignant neoplasm of overlapping sites of left eye and adnexa
C69.90	Malignant neoplasm of unspecified site of unspecified eye
C69.91	Malignant neoplasm of unspecified site of right eye
C69.92	Malignant neoplasm of unspecified site of left eye

VIII. REFERENCES

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Uveal Melanoma

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IX. POLICY HISTORY

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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 01/01/2019. 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 01/01/2021.
	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 04/01/2022
	09/09/2022 Consensus Review. Policy statement unchanged. NCCN language added. FEP language revised. Background, Rationale and References updated.

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12/01/2022 Administrative Update. New Code 0357U added; effective 01/01/2023
07/03/2023 Consensus Review. Policy statements unchanged. References updated. Coding reviewed. Removed 0357U as it is a deleted code.
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 10/01/2024.
11/20/2024 Administrative Update. Removed NCCN statement.
02/18/2025 Minor Review. Removed gene expression profiling for cutaneous melanoma policy criteria and information. Changed policy title to Gene Expression Profiling for Uveal Melanoma. References updated. Coding reviewed and removed codes 0089U, 0090U, 0314U, 0490U, 81529.
06/10/2025 Administrative Update. Removing the Benefit Variations and updating the Disclaimer.
03/06/2026 Retirement Review. Service to be managed by the vendor Evicore

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