Gene Expression Profiling for Uveal Melanoma

Policy # 00548
Original Effective Date: 04/19/2017
Current Effective Date: 11/13/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider gene expression profiling (GEP) for uveal melanoma with DecisionDx-UM®‡ for individuals with newly diagnosed primary, localized uveal melanoma to be **eligible for coverage.****

Note:
Patients with biopsy confirmed localized uveal melanoma may be considered for either GNAQ, GNA11, BAP1, SF3B1, EIF1AX, or PRAME expression testing if requested test was not previously done and is not done in addition to DecisionDx-UM test (e.g., DecisionDx-PRAME, DecisionDx-UMSeq).

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers gene expression profiling (GEP) for uveal melanoma that do not meet the above criteria, including but not limited to repeat testing or testing of individuals with clinical evidence of metastatic disease, to be **investigational.***

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Background/Overview

Uveal Melanoma

The uveal tract is the middle layer of the wall of the eye; it has 3 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 blacks. 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 RCTs 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 [CI], 9% to 12%), 25% (95% CI, 23% to 27%), and 34% (95% CI, 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 the 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 IIIC.

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 3 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 2 distinct types of uveal melanomas—those with monosomy chromosome 3 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 1 study (2016), 89% of tumors with monosomy 3 had a BAP1 variant, and no tumors without monosomy 3 had a BAP1 variant.

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

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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 has chosen not to require any regulatory review of this test.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Uveal melanoma is associated with a high rate of metastatic disease, and survival after the development of metastatic disease is poor. Prognosis following treatment of local disease can be assessed using various factors, including clinical and demographic markers, tumor stage, tumor characteristics, and tumor cytogenetics. Gene expression profiling (GEP) can be used to determine prognosis, and gene expression profile testing is commercially available.

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 6 reported that GEP

classification correlated strongly with metastatic disease and/or 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 of 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.

Supplemental Information

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines (v.1.2023) for uveal melanoma state that “for patients who had a biopsy of their primary tumor, certain molecular features have been shown to be prognostic for risk of distant spread and should be used for risk stratification. Gene expression profiling (GEP) is recommended to determine whether the tumor is Class 1A (low risk), Class 1B (medium risk), or Class 2 (high risk) to inform frequency of follow-up. It has been shown that Class 2 was associated with a 5-fold to 20-fold higher risk of metastasis than Class 1.” Also noted that “GEP class had a stronger independent association with metastasis than any other prognostic factor (P<.0001). Elevated expression of PRAME (PRAME+) could be a risk modifier for metastasis in patients with either Class 1 or Class 2 uveal melanoma.”

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Melanoma Focus
In 2015, Melanoma Focus, a British medical nonprofit that focuses on melanoma research, published guidelines on uveal melanoma. These guidelines, which were created using a process accredited by NICE, contained the following statements on prognosis and surveillance. A 2022 guideline update included several additional relevant statements, which are denoted with (2022).29, A separate update to the guidance for surveillance is underway at the time of this review.

″ 2.5 Genetic and molecular features (2022)

Prognostic factors/tool

28. Prognostic factors of uveal melanoma are multi-factorial and include clinical, morphological and genetic features. The following features should be recorded:

- Age
- Gender
- Tumour location
- Tumour height
- Tumour Largest [sic] basal diameter
- Ciliary body involvement
- Extraocular melanoma growth (macroscopic)

The following features should be recorded if tissue is available:

- Cell type (modified Callender system)
- Mitotic count (number/40 high power fields in H&E [hematoxylin and eosin] stained sections)
- Presence of extravascular matrix patterns (particularly closed connective tissue loops; enhanced with Periodic acid Schiff staining).
- Presence of extraocular melanoma growth (size, presence or absence of encapsulation).
- Positive or negative expression of nuclear BAP1 protein in the tumour cells. (2022)

29. The following features should be recorded if cytology of tumour is available:

- Confirmation of melanoma cells (i.e., exclude differential diagnoses, particularly metastatic carcinoma) - immunocytology may be required for this, but is not always necessary.

- Cell type (modified Callender system), if possible. (2022)

Prognostic biopsy

30. There should be a fully informed discussion with all patients, explaining the role of biopsy including the benefits and risks. The discussion should include:
- Enabling prognostication and allow tailored follow-up
- Allowing recruitment into adjuvant trials
- Risks of having the biopsy
- Limitations of the investigation
- Effects of prognostication information on quality of life (2022)

31. The minimum dataset for uveal melanoma from the Royal College of Pathology (or national official equivalents) should be recorded in the pathology reports. [...]

32. Use the most up-to-date edition of the Tumor Node Metastasis staging system for prognostication and include in pathology/clinical reports. (2022)

33. Collect molecular genetic and/or cytogenetic data for research and prognostication purposes, where tumour material is available and where patient consent has been obtained, as part of an ethically-approved research programme. (2022)

34. The use of multifactorial prognostication models incorporating clinical, histological, immunohistochemical and genetic tumour features should be considered. (2022)

35. Where available the results of state-of-the-art molecular analysis should be combined with clinical features and standard anatomical and pathological staging for prognostication. (2022)

36. Tests for novel circulating blood-borne biomarkers should only be used within clinical trials or research programmes. (2022)

[...]

2.7 Surveillance

40. Prognostication and surveillance should be led by a specialist multidisciplinary team that incorporates expertise from ophthalmology, radiology, oncology, cancer nursing and hepatic services.

41. Prognostication and risk prediction should be based on the best available evidence, taking into account clinical, morphological and genetic cancer features.

42. All patients, irrespective of risk, should have a holistic assessment to discuss the risk, benefits and consequences of entry into a surveillance programme. The discussion should consider risk of false positives, the emotional impact of screening as well as the frequency and duration of screening. An individual plan should be developed.

43. Patients judged at high-risk of developing metastases should have 6-monthly life-long surveillance incorporating a clinical review, nurse specialist support and liver specific imaging by a non-ionising modality.

44. Liver function tests alone are an inadequate tool for surveillance. "

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date

Ongoing			
NCT02376920[a]	5 Year Registry Study to Track Clinical Application of DecisionDx-UM Assay Results and Associated Patient Outcomes (CLEAR)	2800	Apr 2022 (last update posted May 2022)
NCT02068586[a]	A Randomized Phase ll Study of Adjuvant Sunitinib or Valproic Acid in High-Risk Patients With Uveal Melanoma	150	Jun 2023
NCT03528408[a]	Phase II Single-arm Multi-center Study of Adjuvant Ipilimumab in Combination With Nivolumab in Subjects With High-risk Ocular Melanoma	52	Jun 2023
NCT05502900	Adjuvant Melatonin for Uveal Melanoma	100	Jan 2031

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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04/06/2017	Medical Policy Committee review
04/19/2017	Medical Policy Implementation Committee approval. New policy.
04/05/2018	Medical Policy Committee review
04/18/2018	Medical Policy Implementation Committee approval. No change to coverage.
04/04/2019	Medical Policy Committee review
04/24/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/02/2020	Medical Policy Committee review
04/08/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/01/2021	Medical Policy Committee review
04/14/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/05/2022	Medical Policy Committee review
05/11/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Coding update
10/06/2022	Medical Policy Committee review
10/11/2022	Medical Policy Implementation Committee approval. Senate bill update. "Newly diagnosed" added to eligible coverage section. And repeat testing added as investigational. Note added.
10/05/2023	Medical Policy Committee review
10/11/2023	Medical Policy Implementation Committee approval. No change to coverage. Body of policy updated.

Next Scheduled Review Date: 10/2024

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81552
HCPCS	No codes
ICD-10 Diagnosis	C69.30-C69.32, C69.40-C69.42, C69.80-C69.82, C69.90-C69.92

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.