



Louisiana

Gene Expression Profiling for Uveal Melanoma

Policy # 00548

Original Effective Date: 04/19/2017

Current Effective Date: 05/10/2021

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 patients with primary, localized uveal melanoma to be **eligible for coverage.****

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 to be **investigational.***

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

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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.

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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 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.

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.

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

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Rationale/Source

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.

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. Three studies of clinical validity identified used the GEP score to predict melanoma metastases and melanoma-specific survival. All 3 reported that GEP classification correlated strongly with metastatic disease and melanoma mortality. Two 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.

Supplemental Information

Practice Guidelines and Position Statements

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National Comprehensive Cancer Network

In the (v.1.2019) National Comprehensive Cancer Network guidelines for uveal melanoma state that biopsy specimens 'should be sent for histology, chromosome analysis, and/or gene expression profiling.' The guidelines include DecisionDx-UM classes as 1 of the factors used to risk-stratify patients for systemic imaging.

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 the National Institute for Health and Care Excellence, contained the following statements on prognosis and surveillance.

“3.5.1 Prognostic factors/tools

1. 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). Grade A
- Presence of extraocular melanoma growth (size, presence or absence of encapsulation). [GRADE A]

3.5.2 Prognostic biopsy

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1. There should be a fully informed discussion with all patients, explaining the role of biopsy including the benefits and risks. The discussion should include:
 - o Risk of having the biopsy
 - o Limitations of the investigation
 - o Benefits for future treatments (including possible recruitment to trials)
 - o Impact on quality of life...
 - o Follow-up [GPP]...
2. Use of the current (i.e. 7th) Edition of the TN staging system for prognostication is highly recommended. Grade A
3. Use of multifactorial prognostication models incorporating clinical, histological, immunohistochemical and genetic tumour features - should be considered. Grade D

3.6 Surveillance

1. Prognostication and surveillance should be led by a specialist multidisciplinary team that incorporates expertise from ophthalmology, radiology, oncology, cancer nursing and hepatic services. [GPP]
2. Prognostication and risk prediction should be based on the best available evidence, taking into account clinical, morphological and genetic cancer features. [GPP]
3. 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. [GPP]
4. 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. [GPP] ...
5. Liver function tests alone are an inadequate tool for surveillance. Grade C”

Note that Melanoma Focus defined GPP as a recommended best practice based on the clinical experience of the guideline development group. A guideline update is in progress at the time of this review.

U.S. Preventive Services Task Force Recommendations

Not applicable.

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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 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT02376920 ^a	5 Year Registry Study to Track Clinical Application of DecisionDx-UM Assay Results and Associated Patient Outcomes (CLEAR)	2800	Oct 2020
NCT02068586 ^a	A Randomized Phase II Study of Adjuvant Sunitinib or Valproic Acid in High-Risk Patients With Uveal Melanoma	150	Dec 2021 (recruiting)
NCT02223819 ^a	Phase II Trial of Adjuvant Crizotinib in High-Risk Uveal Melanoma Following Definitive Therapy	34	Aug 2022
NCT03528408 ^a	Phase II Single-arm Multi-center Study of Adjuvant Ipilimumab in Combination With Nivolumab in Subjects With High-risk Ocular Melanoma	50	Jun 2023 (recruiting)

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.

Next Scheduled Review Date: 04/2022

Coding

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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	81522, 81552
HCPCS	No codes
ICD-10 Diagnosis	C69.30-C69.32, C69.40-C69.42, C69.80-C69.82

*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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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.

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****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.

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