Gene Expression Profiling for Uveal Melanoma

Policy # 00548
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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 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 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 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. The DecisionDx-UM test (Castle Biosciences, Phoenix, AZ) is 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. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

UVEAL MELANOMA
Clinical Context and Test Purpose
The purpose of using the DecisionDx-UM test in individuals with localized uveal melanoma is to inform a decision about how often patients should undergo follow-up for metastases, based on their likelihood of developing metastases.

The optimal method and interval for surveillance are not well-defined, and it has not been established in prospective trials whether surveillance identifies metastatic disease earlier. Potential methods for metastases include magnetic resonance imaging, ultrasound, liver function testing, and positron emission

tomography scans. One retrospective study (2016) of 262 patients estimated that use of hepatic ultrasound and liver function testing every 6 months in individuals with treated local uveal melanoma would yield a sensitivity and specificity for a diagnosis of metastasis of 83% (95% confidence interval [CI], 44% to 97%) and 100% (95% CI, 99% to 100%), respectively.

Identifying patients at high-risk for metastatic disease might assist in selecting patients for adjuvant treatment and more intensive surveillance for metastatic disease, if such changes lead to improved outcomes. Adjuvant treatment for metastatic disease consists of radiotherapy or systemic therapy, such as chemotherapy, immunotherapy, hormone therapy, biologic therapy, or targeted therapy. Randomized trials of patients with high-risk for uveal melanoma recurrence have shown no differences in survival rates between patients treated with and without adjuvant therapy. However, these trials were reported in 1990 and 1998, and may not represent current treatment and risk stratification methods.

Identifying patients at low-risk for metastatic disease might assist in selecting patients who could safely reduce frequency or intensity of surveillance, which could lead to improved outcomes through reduced burden.
The question addressed in this evidence review is: Does gene expression profile testing to determine the prognosis of patients with uveal melanoma improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with localized uveal melanoma.

Uveal melanomas may present with visual symptoms or be detected incidentally. The diagnosis is based on funduscopic examination and other noninvasive tests, such as ultrasound and fluorescein angiography. A biopsy may be useful to collect additional information about the molecular characteristics of the tumor. Treatment of primary, localized uveal melanoma can be by surgery or radiotherapy. While treatment is effective at preventing local recurrence, patients are at risk for distant metastases for many years. Approximately 50% of patients will develop distant metastasis, which is the leading cause of death in patients with uveal melanoma.

Interventions
The test being considered is DecisionDx-UM.

DecisionDx-UM is a GEP test intended to assess 5-year metastatic risk in uveal melanoma. The test was introduced in 2009 and claims to identify the molecular signature of a tumor and its likelihood of metastasis within 5 years. The assay determines the expression of 15 genes, which stratify a patient's risk of metastasis into 3 classes. The 15-gene signature was originally developed based on a hybridization-based microarray platform; the current commercially available version of the DecisionDx-UM test is a polymerase chain reaction–based test that can be performed on fine-needle aspirate samples.

Based on the clinical outcomes from the prospective, 5-year multicenter Collaborative Ocular Oncology Group study, the DecisionDx-UM test reports class 1A, class 1B, and class 2 phenotypes:

Class 1A: Very low-risk, with a 2% chance of the eye cancer spreading over the next 5 years;
Class 1B: Low-risk, with a 21% chance of metastasis over 5 years;
Class 2: High-risk, with 72% odds of metastasis within 5 years.

Comparators

National Comprehensive Cancer Network guidelines for melanoma do not address the prognosis and management of uveal melanoma. Melanoma Focus (2015), a British medical nonprofit that focuses on melanoma research, published guidelines on uveal melanoma that state that prognostication and risk prediction should be based clinical, morphologic, and genetic cancer features.

Outcomes

The potential beneficial outcome associated with selecting high-risk patients for adjuvant treatment and more intensive surveillance for metastatic disease is improved survival while potential harmful outcomes are related to adverse events of treatment and increased burden of surveillance.

The potential beneficial outcome associated with selecting low-risk patients for less intensive surveillance for metastatic disease is reduced burden; potential harmful outcomes are related to delayed detection of metastasis.

Timing

Distant metastasis can develop years or even decades after local treatment of uveal melanoma.

Setting

Patients are usually diagnosed by an optometrist or ophthalmologist and referred to a specialist ocular oncologist. The management of uveal melanoma is complex and may require a multidisciplinary team of specialists.

Simplifying Test Terms

There are 3 core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful.

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or to predicting a response to therapy.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Three studies have reported data on the association between GEP score and clinical outcomes; they are summarized in Table 1. All studies showed strong and positive associations between GEP classification and clinical outcomes.

The first study was published by Onken et al (2012). This prospective, multicenter study evaluated the prognostic performance of a 15-gene GEP assay in patients with posterior (choroidal and ciliary body) uveal melanoma. Prognostic groups were class 1 (low-risk of metastasis) or class 2 (high-risk of metastasis). A total of 459 cases were enrolled from 12 centers between June 2006 and November 2010. The GEP assay rendered a classification in 97.2% of cases. GEP test results were class 1 in 276 (61.9%) cases and class 2 in 170 (38.1%) cases. Mean follow-up was 18.0 months (median, 17.4 months). Metastasis was detected in 3 (1.1%) of class 1 cases and 44 (25.9%) of class 2 cases ($p < 0.001$). By univariate Cox proportional hazard analysis, factors associated with metastatic disease included advanced patient age ($p=0.02$), ciliary body involvement ($p=0.03$), tumor diameter ($p<0.001$), tumor thickness ($p=0.006$), chromosome 3 status ($p<0.001$), and GEP class ($p<0.001$). The GEP test was associated with a significant net reclassification index over TNM classification for survival at 2 years (NRI=0.37, $p=0.008$) and 3 years (NRI=0.43, $p=0.001$).
Two other studies reporting data on clinical validity were published in 2016. Walter et al evaluated 2 cohorts of patients at 2 clinical centers who underwent resection for uveal melanoma. This study had a similar methodology to Onken (2012). The primary cohort included 339 patients, of which 132 patients were also included in the Onken (2012) study, along with a validation cohort of 241 patients, of which 132 were also included in the Onken study, the latter group of which was used to test a prediction model using the GEP

plus pretreatment largest basal diameter. Cox proportional hazards analysis, was used in the primary cohort to examine GEP classification and other clinicopathologic factors (tumor diameter, tumor thickness, age, sex, ciliary body involvement, pathologic class). GEP class 2 was the strongest predictor of metastases and mortality. Tumor diameter was also an independent predictor of outcomes, using a diameter of 12 mm as the cutoff value. In the validation cohort, GEP results were class 1 (61.4%) in 148 patients and class 2 (38.6%) in 93 patients. Again, GEP results were most strongly associated with progression-free survival.

Decatur et al (2016) was a smaller, retrospective study of 81 patients who had tumor samples available from resections occurring between 1998 and 2014. GEP was class 1 in 35 (43%) patients, class 2 in 42 (52%) patients, and unknown in 4 (5%) patients. GEP class 2 was strongly associated with *BAP1* variants (r=0.70; p<0.001). On Cox proportional hazards analysis, GEP class 2 was the strongest predictor of metastases and melanoma mortality (see Table 1).

Table 1. Studies of Clinical Validity

Study	Patient Populations	Rates of Metastases		Melanoma Mortality Rates	
		GEP Class 1	GEP Class 2	GEP Class 1	GEP Class 2
Onken (2012)	459 patients with UM from 12 clinical centers	1.1%	25.9%[a]	NR	NR
Walter (2016)	Primary cohort: 339 patients from 2 clinical centers with UM arising in ciliary body or choroid	5.8%	39.6%	3.7%	29.5%
	Validation cohort: 241 patients from 2 clinical centers with UM arising in ciliary body or choroid	2.7%	31.2%	0.7%	17.2%
Decatur (2016)	81 patients from a single center with available UM tumor samples arising from ciliary body or choroid		9.4[a,b] (3.1 to 28.5)		15.7[a,b] (3.6 to 69.1)

GEP: gene expression profile; NR: not reported; UM: uveal melanoma.

[a] p<0.001.

[b] Reported as relative risk (95% confidence interval) for metastases (or melanoma mortality) in group 2 vs group 1.

Section Summary: Clinically Valid

Three published studies on clinical validity were included in this review. These studies have reported that GEP class 2 is a strong predictor of metastases and melanoma survival, and also strongly correlates with *PAB1* variants. Two studies have compared GEP class with clinicopathologic features and have reported that GEP classification is the strongest predictor of clinical outcomes.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

There is no direct evidence that use of DecisionDx-UM for the selection of patients for different surveillance outcomes improves health outcomes. Absent direct evidence, a chain of evidence can be developed based on the clinical validity of the test.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The GEP test is associated with risk of metastatic disease and melanoma death. Although the three available studies reporting on clinical validity do not all specifically report on rates of survival or metastasis risk by risk group, there is clearly an association between risk category and metastasis and death. For a rare cancer, the studies on clinical validity include a large proportion of annual incident cases.

Plasseraud et al (2016) reported on metastasis surveillance practices and patient outcomes using data from a prospective observational registry study of DecisionDx-UM conducted at 4 centers, which included 70 patients at the time of reporting. Surveillance regimens were documented by participating physicians as part of registry data entry. “High-intensity” surveillance was considered to be imaging and/or liver function testing every 3 to 6 months and “low-intensity” surveillance was considered to be annual imaging and/or liver function testing. The method for following patients for clinical outcomes was not specified. Of the 70 enrolled patients, 37 (53%) were class 1. Over a median follow-up of 2.38 years, more class 2 patients (36%) than class 1 patients (5%; p=0.002) experienced a metastasis. The 3-year metastasis-free survival rate was lower for class 2 patients (63%; 95% CI, 43% to 83%) than class 1 patients (100%; CI not specified; p=0.003). Most class 1 patients (n=30) had low-intensity surveillance and all (n=33) class 2 patients had high-intensity surveillance. 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 were collected, making the risk of bias high.

Aaberg et al (2014) reported on changes in management associated with GEP risk classification. They analyzed Medicare claims data submitted to Castle Biosciences by 37 ocular oncologists in the United States. Data were abstracted from charts on demographics, tumor pathology and diagnosis, and clinical surveillance patterns. High-intensity surveillance was defined as a frequency of every 3 to 6 months, and low-intensity surveillance was a frequency of every 6 to 12 months. Of 195 patients with GEP test results, 88 (45.1%) patients had evaluable tests and adequate information on follow-up surveillance, 36 (18.5%) had evaluable tests and adequate information on referrals, and 8 (4.1%) had evaluable tests and adequate

information on adjunctive treatment recommendations. Of the 191 evaluable GEP tests, 110 (58%) were class 1, and 81 (42%) were class 2. For patients with surveillance data available (n=88), all patients in GEP class 1 had low-intensity surveillance and all patients in GEP class 2 had high-intensity surveillance ($p<0.001$ vs class 1).

It is likely that treating liver metastasis affects local symptoms and survival, for at least a subset of patients. However, it is uncertain whether the surveillance interval has an effect on the time to detection of metastases.

There is the potential for patients considered to be at high-risk for metastases to undergo adjuvant treatment, but to date, no adjuvant therapies for nonmetastasized uveal melanomas have been shown to reduce the risk of metastasis.

Section Summary: Clinically Useful
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. GEP classification appears to be a strong predictor metastatic disease and melanoma death. 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 or through the detection of metastases earlier. However, classification into the low-risk group would permit a reduction in the burden of surveillance without apparent harm.

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. Three studies of clinical validity identified used the GEP score to predict melanoma metastases and melanoma-specific survival. All three 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 a meaningful improvement in the net health outcome.

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Policy History

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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.
Next Scheduled Review Date: 04/2019

Coding

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Code Type	Code
CPT	81599, 84999

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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. 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.

**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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