Gene Expression Profiling has been proposed as a method of risk stratification for uveal melanoma.

**Background**

**Uveal melanoma**

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 Caucasians, 0.9 among Hispanics and 0.24 among African-Americans.

Uveal melanoma has a progressively rising, age-specific, incidence rate that peaks near the age of 70 years. Host susceptibility factors associated with the development of this cancer include Caucasian race, fair skin and light eye color.

The uveal tract is the middle layer of the wall of the eye, and has three main parts: the choroid (a tissue layer filled with blood vessels), the 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. Iris melanomas have the best prognosis; melanomas of the ciliary body have the worst prognosis.

**Clinical diagnosis/prognosis**

Modern diagnostic tools, including indirect fundoscopic examination, optical coherence tomography, computed tomography (CT), and magnetic resonance imaging (MRI) of the globe and orbital tissues, have led to significant advances in the ability to diagnose primary uveal melanoma. The clinical diagnosis of uveal melanoma has an accuracy of 99%, and therefore, biopsies and/or tumor resection with histopathologic examination are not essential for diagnosis.

Metastatic disease is the leading cause of death in patients with uveal melanoma, and approximately 50% of patients will develop distant metastasis. The most important clinical factors that predict metastatic disease are tumor size measured in diameter or in thickness, ciliary body involvement and transcleral extension.

Genetic analysis of uveal melanoma can provide prognostic information for the risk of developing metastatic disease. In 1996, Prescher and colleagues showed that monosomy of chromosome 3 correlated strongly with metastatic death, with a 5-year survival reduction from 100% to 50%. Subsequent studies reported the initial idea that, based on genetic analysis, there were two 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.

Genetic 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.
Gene Expression Profiling for Uveal Melanoma

**Treatment**

Local treatment of uveal melanoma is well-established and is termed “conservative” if conservation of the eye is attempted. Conservative treatments include brachytherapy and external (proton beam) irradiation. “Radical” therapy consists of enucleation. Both strategies offer the same prognosis, both in terms of survival rates and risk of metastasis, as shown by the randomized trials from the Collaborative Ocular Melanoma Study (COMS).

However, despite the established treatment protocols for primary uveal melanoma, no decrease in the mortality rate of this tumor has been observed. The 5-year survival rate has not changed over the last 3 decades (81.6%), suggesting that life expectancy is independent of successful local eye treatment. Therefore, it has been suggested that the identification of patients at high risk of metastatic disease may assist in selecting patients that might benefit from adjuvant treatment, or that regular screening for the presence of metastatic disease may lead to improved outcomes. Adjuvant treatment may consist of radiotherapy or systemic therapy, such as chemotherapy, immunotherapy, hormone therapy, biological therapy or target therapy. However, randomized trials of patients with high risk of uveal melanoma recurrence showed no difference in survival between patients treated with adjuvant therapy versus no adjuvant treatment. In addition, regular screening tests for the development of liver metastases, including measurement of liver function tests, liver ultrasound, CT scan or MRI, have not shown evidence of any effect on patient outcomes.

The clinical course of patients with hepatic metastases is highly dependent on disease progression in the liver, and treatment of hepatic metastases has shown to be associated with prolonged survival in some patients. Therapies directed at loco-regional treatment of hepatic metastases include surgical and ablative techniques, embolization and local chemotherapy.

**Commercially available testing:**

The DecisionDx-UM test (Castle Biosciences Inc, Phoenix, AZ) is a gene expression profile (GEP) test intended to assess five-year metastatic risk in uveal melanoma. The test was introduced in late 2009, and claims to identify the molecular signature of a tumor and its likelihood of metastasis within five years. The assay determines the expression of 15 genes which stratify a patient’s individual risk of metastasis into two classes.

Based upon the clinical outcomes from the prospective, 5-year multi-center Collaborative Ocular Oncology Group (COOG) study, the DecisionDx-UM test reports Class 1A, Class 1B and Class 2 phenotype:

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

**Regulatory Status**

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).

**Related policy:**

Charged Particle Radiotherapy (Proton or Helium Ion)

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy
Gene Expression Profiling for Uveal Melanoma

Gene Expression Profiling for Uveal Melanoma is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Gene Expression Profiling for Uveal Melanoma is covered

Not applicable.

When Gene Expression Profiling for Uveal Melanoma is not covered

Gene expression profiling for uveal melanoma is considered investigational. BCBSNC does not provide coverage for investigational services or procedures.

Policy Guidelines

Uveal melanoma is associated with a high rate of metastatic disease, predominantly to the liver. Survival after the development of metastatic disease is poor. Certain clinical factors and tumor genetic alterations are used to determine risk of metastases in individual patients, although it has not been shown that adjuvant treatment for patients who are considered to be at high risk for metastases alters survival outcomes, nor has it been shown that screening for the detection of early metastases has any effect on patient outcomes.

Gene expression profiling has been proposed as another method to risk-stratify patients, and preliminary studies have suggested that it may accurately identify patients at high risk for developing metastases. However, the clinical utility of the test has not been established, therefore it is considered investigational.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: No specific code

The unlisted multianalyte assays with algorithmic analyses code 81599 or the unlisted chemistry procedure code 84999 may be reported.

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.
Gene Expression Profiling for Uveal Melanoma

Scientific Background and Reference Sources


Policy Implementation/Update Information

7/15/14 New medical policy issued. Gene expression profiling for uveal melanoma is considered investigational. Reviewed with Sr. Medical Director 7/2014. (lpr)

7/28/15 Specialty Matched Consultant Advisory Panel review 6/24/2015. Reference added. No change to policy statement. (lpr)

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