Medical Policy
Gene Expression Profiling for Uveal Melanoma

Table of Contents
- Policy: Commercial
- Policy: Medicare
- Authorization Information
- Coding Information
- Description
- Policy History
- Information Pertaining to All Policies
- References

Policy Number: 683
BCBSA Reference Number: 2.04.120

Related Policies
- Charged-Particle (Proton or Helium Ion) Radiation Therapy, #437

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue™ and Medicare PPO Blue™ Members

Gene expression profiling for uveal melanoma is INVESTIGATIONAL.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required for outpatient services.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.

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<th>Commercial Managed Care (HMO and POS)</th>
<th>Commercial PPO and Indemnity</th>
<th>Medicare HMO Blue™</th>
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CPT Codes / HCPCS Codes / ICD-9 Codes
The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.
**CPT Codes**
No specific CPT codes

**Description**
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 whites, 0.9 among Hispanics and 0.24 among blacks.(1)

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 white race, fair skin and light eye color.

The uveal tract is the middle layer of the wall of the eye, and 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.(1) 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.(2)

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 et al showed that monosomy of chromosome 3 correlated strongly with metastatic death, with a 5-year survival reduction from 100% to 50%.(3) Subsequent studies reported the initial idea 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.(1)

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.

**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.(1) “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).(4)

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.(2) Therefore, it has been suggested that the identification of patients at high risk of metastatic disease may assist in selecting patients who 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.(5)

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 for:
The DecisionDx-UM® test (Castle Biosciences Inc, Phoenix, AZ) is a GEP test intended to assess 5-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 5 years. The assay determines the expression of 15 genes, which stratify a patient’s individual risk of metastasis into 2 classes.

Based on the clinical outcomes from the prospective, 5-year multicenter 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 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.

Summary
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, and it is considered investigational.

Policy History

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Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

References