Gene Expression Profiling for 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.

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 have shown that radiotherapy and enucleation have equivalent rates of metastatic disease. Radiotherapy can be delivered by a variety of 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.

Survveillance for 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 (COMS) study 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
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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.

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 2016 retrospective study 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% CI, 44% to 97%) and 100% (95% CI, 99% to 100%), respectively.

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

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 in thickness, ciliary body involvement and transcleral extension.

Clinical staging according to the American Joint Committee on Cancer (AJCC) recommendations allows risk stratification for metastatic disease. In a retrospective study of 3377 patients with uveal melanoma, in which staging was performed using AJCC classifications, the rate of metastases-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 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. The BAP1 gene has been identified as an important marker of disease type. In 1 study, 89% of tumors with monosomy 3 had a BAP1 mutation, and no tumors without monosomy 3 had a BAP1 mutation

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.

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 three classes. The 15 gene signature was originally developed based on a hybridization-based microarray platform; the currently commercially-available DecisionDx-UM test is a polymerase chain reaction (PCR)-based test that can be performed on fine-needle aspiration samples.
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Based on 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 phenotypes:

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.

Related policy:
Charged Particle Radiotherapy

***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

BCBSNC will provide coverage for gene expression profiling for uveal melanoma when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

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

Gene expression profiling for uveal melanoma with DecisionDx-UM is considered medically necessary for patients with primary, localized uveal melanoma.

When Gene Expression Profiling for Uveal Melanoma is not covered

Gene expression profiling for uveal melanoma that does not meet the above criteria is considered investigational.

Policy 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. This evidence review addresses whether outcomes are improved when GEP testing is used to determine prognosis of patients with uveal melanoma compared to determining prognosis without GEP testing.

For individuals who have localized uveal melanoma who receive a GEP test for uveal melanoma, 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. There is limited published data on the analytic validity of GEP testing. Three studies of clinical validity identified used the GEP score to predict melanoma metastases and survival. All 3 reported that GEP class correlated strongly with metastatic disease and melanoma mortality. Two studies compared GEP class to other prognostic markers, and GEP class had the strongest association among the markers tested. GEP classification appears 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...
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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 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.

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 reimburséd. 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.

Scientific Background and Reference Sources


Sr. Medical director review 7/2014

Specialty Matched Consultant Advisory Panel review- 6/2015

Sr. Medical Director review 2/2017
Gene Expression Profiling for Uveal Melanoma

Specialty Matched Consultant Advisory Panel review- 6/2017

Policy Implementation/Update Information

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
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<tr>
<td>7/15/14</td>
<td>New medical policy issued. Gene expression profiling for uveal melanoma is considered investigational. Reviewed with Sr. Medical Director 7/2014. (lpr)</td>
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<tr>
<td>7/28/15</td>
<td>Specialty Matched Consultant Advisory Panel review 6/24/2015. Reference added. No change to policy statement. (lpr)</td>
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<tr>
<td>7/26/16</td>
<td>Specialty Matched Consultant Advisory Panel review 6/29/2016. Updated Description and Policy Guidelines sections. Reference added. No change to policy statement. (lpr)</td>
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<tr>
<td>3/31/17</td>
<td>Policy statement changed to medically necessary for patients with localized uveal melanoma under “When Covered” section: “Gene expression profiling for uveal melanoma with DecisionDx-UM is considered medically necessary for patients with primary, localized uveal melanoma.” Updated Description and Policy Guidelines sections. Reference added. Sr. Medical Director review 2/2017. (lpr)</td>
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<tr>
<td>7/28/17</td>
<td>Specialty Matched Consultant Advisory Panel review 6/28/2017. No change to policy statement. (lpr)</td>
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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.