Introduction

Uveal melanoma is a rare cancer of the eye that often spreads to other parts of the body. A special type of genetic testing called “gene expression profiling” (GEP) looks at the activity of many genes at once to give a broad picture of cellular function in a tumor. It has been used to help determine the prognosis of a person with uveal melanoma. This policy describes when gene expression profiling may be medically necessary in cases of uveal melanoma.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Service</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene expression profiling, uveal melanoma</td>
<td>Gene expression profiling for uveal melanoma with DecisionDx-UM® is medically necessary for patients with primary, localized uveal melanoma.</td>
</tr>
</tbody>
</table>
Examples of commercial tests include:
- DecisionDx-UM® test (Castle Biosciences Inc., Phoenix, AZ)

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

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
</tbody>
</table>

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N/A

Description

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.

Background

**Uveal melanoma**

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.\(^1\)

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 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.\(^2,3\) Radiotherapy can be delivered by various mechanisms, most commonly brachytherapy and proton beam therapy.\(^1,2\) 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.\(^4\)

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.
**Surveillance 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. However, they are at risk for distant metastases, particularly to the liver, for years after presentation. The prospective, longitudinal Collaborative Ocular Melanoma Study (COMS) 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.

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 detecting metastases include magnetic resonance imaging, ultrasound, liver function testing, and positron emission tomography scans. One 2016 retrospective study of 262 patients estimated that the 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 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, biological therapy, or targeted therapy. Randomized trials of patients with a 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 1998 and 1990, and may not be representative of current treatment 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 transscleral 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

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%. 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. 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.

Gene 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

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 individual 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.

Summary of Evidence

For individuals who have localized uveal melanoma who receive a gene expression profiling (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 (DecisionDx-UM) has published data related to its clinical validity, and is the focus of this review. There is limited published data on the analytic validity of GEP testing. Three studies of clinical validity 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 to 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 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.

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

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
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<tr>
<td>NCT02376920</td>
<td>5 Year Registry Study to Track Clinical Application of DecisionDx-UM Assay Results and Associated Patient Outcomes (CLEAR)</td>
<td>2800</td>
<td>Oct 2020</td>
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</tbody>
</table>

NCT: national clinical trial.

Practice Guidelines and Position Statements

**National Comprehensive Cancer Network**

In its guidelines on melanoma (v.1.2017), the National Comprehensive Cancer Network (NCCN) states: “Mucosal and uveal melanomas differ significantly from cutaneous melanoma in presentation, genetic profile, staging, response to treatment, and patterns of progression. Ideally, mucosal and uveal melanoma should be treated as diseases distinct from cutaneous melanoma, with care tailored to the individual.”

**Melanoma Focus**

Melanoma Focus, a British medical nonprofit that focuses on melanoma research, published guidelines on uveal melanoma in 2015. 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
2. 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

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:
   - Risk of having the biopsy
   - Limitations of the investigation
   - Benefits for future treatments (including possible recruitment to trials)
   - Impact on quality of life
   - Recruitment to trials
   - Follow-up [GPP]

2. The minimum dataset for uveal melanoma from the Royal College of Pathology should be recorded. [https://www.rcpath.org/asset/44EB109E-3E3D-4704-B7B57F86F657BA09/](https://www.rcpath.org/asset/44EB109E-3E3D-4704-B7B57F86F657BA09/) Grade D

3. Tests for novel serological biomarkers should only be used within clinical trials or research programmes. [GPP]
4. Consider collecting molecular genetic and/or cytogenetic data for research and prognostication purposes where tumour material is available and where patient consent has been obtained as part of an ethically approved research programme. [GPP]

5. Use of the current (ie, 7th) Edition of the TNM staging system for prognostication is highly recommended. Grade A

6. 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: Melanoma Focus defined GPP as: recommended best practice based on the clinical experience of the guideline development group.

### Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.
Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). The DecisionDx-UM® test is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

References


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/11/14</td>
<td>New Policy. Policy created with a literature review through March 11, 2014. Gene expression profiling for uveal melanoma is considered investigational.</td>
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<tr>
<td>07/14/15</td>
<td>Annual Review. Policy updated with literature review through April 28, 2015; no references added. Policy statement unchanged.</td>
</tr>
<tr>
<td>10/01/16</td>
<td>Annual Review, approved September 13, 2016. Policy updated with literature review through April 29, 2016; references 2-4, 6-9, 11, 14, and 16-18 added. Policy statement unchanged.</td>
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<tr>
<td>05/01/17</td>
<td>Annual review, approved April 11, 2017. Policy updated with literature review through February 2, 2017; references 5-7, 22, and 24 added. Policy statement changed from investigational to medically necessary for patients with primary, localized uveal melanoma.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
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<td>-------------------------------------------------</td>
</tr>
<tr>
<td>09/22/17</td>
<td>Policy moved to new format; no change to policy statements.</td>
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200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at
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Office for Civil Rights Complaint Portal, available at
https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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Deutsche (German):

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