Gene Expression Profiling for Uveal Melanoma

Policy # 00548
Original Effective Date: 04/19/2017
Current Effective Date: 04/19/2017

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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 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.

**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, 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 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 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 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 using the American Joint Committee on Cancer (AJCC) recommendations allows risk stratification for metastatic disease. In a 2015 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 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.

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.

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 (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). The DecisionDx-UM test (Castle Biosciences, Phoenix, AZ) 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. 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
The primary question addressed by this review is whether the use of GEP testing to determine prognosis following initial treatment of uveal melanoma improves health outcomes compared to determining prognosis by alternative approaches.

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.

Analytic Validity
Augsburger et al (2015) reported on the correlation between GEP classifications when samples from 2 sites from the same tumor were tested. This prospective, single-center study enrolled 80 patients who had uveal melanoma resection. Tumor samples were taken from 2 different sites and GEP testing was performed independently on both samples. The primary measure reported was the rate of discordance between the 2 samples on GEP class. Nine (11.3%) cases (95% confidence interval [CI], 9.0% to 13.6%) were definitely discordant and 13 (16.3%) cases were definitely or possibly discordant (95% CI, 13.0% to 19.6%). Thus the heterogeneity of tumor and limitations to sampling may explain cases of misclassification where GEP results do not accurately predict prognosis.

In 2010, Onken et al revalidated the GEP assay when it was migrated from a microarray platform to a polymerase chain reaction–based 15-gene assay comprised of 12 discriminating genes and 3 endogenous control genes from previously published data sets. Technical performance of the assay was analyzed in a prospective study of 609 previously untreated tumors. Tumor samples were obtained by fine-needle aspiration (n=553) or after enucleation (n=56). Samples were used for cytologic examination and RNA analysis. The genes were tested on the authors’ training set of 28 uveal melanomas (15 considered to be of prognostic class 1 and 13 in class 2), with clinical follow-up of at least 5 years. The gene assay was demonstrated to be of sufficient sensitivity, failing on 1 of 51 samples with a cytologic diagnosis of quantity not sufficient, and preliminary outcome data affirmed the prognostic accuracy of the assay. The authors concluded, based on preliminary outcome data available for samples collected from 172 patients with a median follow-up of 16 months, that the assay identified which patients would develop metastatic disease (p=1.9×10⁻⁶).

Section Summary: Analytic Validity
There is little published data on the analytic validity of GEP testing. One study has reported validation data of tumor samples from 172 patients using preliminary outcomes data over a median of 16 months as well as results from a training set of 28 samples with at least 5-year follow-up. A second study examined the discordance in GEP classification when 2 samples of the same tumor were tested, and reported discordance in 11.3% to 16.3% of cases. However, this design is more informative of sampling issues in the
face of tumor heterogeneity and does not address the main question of analytic validity: Does repeated testing of the same sample yields confirmatory or discordant results?

Clinical Validity

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 in 2012 by Onken et al. 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). 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 testing 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 (NRI) 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 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Populations</th>
<th>GEP Class 1</th>
<th>GEP Class 2</th>
<th>GEP Class 1</th>
<th>GEP Class 2</th>
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<tr>
<td>Onken et al</td>
<td>459</td>
<td>276 (61.9%)</td>
<td>170 (38.1%)</td>
<td>3 (1.1%)</td>
<td>44 (25.9%)</td>
</tr>
<tr>
<td>Walter et al</td>
<td>339</td>
<td>132 (39.0%)</td>
<td>207 (61.0%)</td>
<td>3 (1.1%)</td>
<td>30 (9.0%)</td>
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<tr>
<td>Decatur et al</td>
<td>81</td>
<td>35 (43%)</td>
<td>42 (52%)</td>
<td>4 (5%)</td>
<td>3 (4%)</td>
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</table>

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| Onken (2012) | 459 pts with UM from 12 clinical centers | 1.1% | 25.9%<sup>a</sup> | NR | NR |
| Walter (2016) | Primary cohort: 339 pts 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 pts from a single center with available tumor samples of UM arising from ciliary body or choroid | 9.4<sup>a,b</sup> | (3.1 to 28.5) | 15.7<sup>a,b</sup> | (3.6 to 69.1) |

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

<sup>a</sup>p<0.001.

<sup>b</sup>Reported as relative risk (95% confidence interval) for metastases (or melanoma mortality) in group 2 vs group 1.

**Section Summary: Clinical Validity**

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 mutations. Two studies have compared GEP class to clinicopathologic features and have reported that GEP classification is the strongest predictor of clinical outcomes.

**Clinical Utility**

Direct evidence of clinical utility is provided by studies that compare health outcomes for patients managed with and without the test. Preferred evidence comes 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.

The GEP test is associated with risk of metastatic disease and melanoma death. Although the 3 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 of risk category and metastasis and death. For a rare cancer, the studies on clinical validity include a large proportion annual incident cases.

Plaserraud et al (2016) reported 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 (LFTs) every 3 to 6 months and “low-intensity” surveillance was considered to be annual imaging and/or LFTs. 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 (MFS) 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.
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 was 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 has an effect on 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: Clinical Utility
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 of 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 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. 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 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 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.

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Original Effective Date: 04/19/2017
Current Effective Date: 04/19/2017
04/06/2017 Medical Policy Committee review
04/19/2017 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 04/2018

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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.

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