Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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(See policy history boxes for previous effective dates)

Title: Genetic Testing-Gene Expression Profiling for Uveal Melanoma

Description/Background

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, and gene expression profile testing is commercially available.

UVEAL MELANOMA

The uveal tract is the middle layer of the wall of the eye; it has three 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 White individuals, 0.9 among Hispanic individuals and 0.24 among Black individuals.(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 have shown that patients receiving radiotherapy

or enucleation progress to metastatic disease at similar rates after treatment.(1,2) Radiotherapy can be delivered by various mechanisms, most commonly brachytherapy and proton beam therapy.(1,3) 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.(2)

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.

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 are at risk for distant metastases, particularly to the liver, for years after presentation.(4) The prospective, longitudinal Collaborative Ocular Melanoma Study (2005) followed 2320 patients with choroidal melanoma with no melanoma metastasis at baseline who were enrolled in randomized controlled trials to evaluate forms of radiotherapy for choroidal melanoma for 5 to 10 years.(5) During follow-up, 739 patients were diagnosed with at least one site of metastasis, of which 660 (89%) were liver. Kaplan-Meier estimates of 2-, 5-, and 10-year metastasis rates were 10% (95% CI, 9% to 12%), 25% (95% CI, 23% to 27%), and 34% (95% CI, 32% to 37%), respectively.

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.(6,7) The most important clinical factors that predict metastatic disease are tumor size (measured in diameter or thickness), ciliary body involvement, and transscleral extension. Clinical staging using the American Joint Committee on Cancer recommendations allows risk stratification for metastatic disease. In a retrospective study of 3377 patients with uveal melanoma (2015), in which staging was performed using American Joint Committee on Cancer classifications, the rate of metastases-free survival at five 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 IIIC.(8,9)

Genetic Analysis

Genetic analysis of uveal melanoma can provide prognostic information for the risk of developing metastatic disease. Prescher et al (1996) showed that monosomy of chromosome 3 correlated strongly with metastatic death, with a 5-year survival reduction from 100% to 50%.(9) Subsequent studies reported 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.(1) The *BAP1* gene has been identified as an important marker of disease type. In one study (2016), 89% of tumors with monosomy 3 had a *BAP1* variant, and no tumors without monosomy 3 had a *BAP1* variant.(10)

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.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests 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 laboratory-developed tests 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.

Medical Policy Statement

The safety and effectiveness of gene-expression profiling for uveal melanoma have been established. It may be considered a useful prognostic tool when indicated.

Inclusionary and Exclusionary Guidelines

Inclusions

- Gene expression profiling for uveal melanoma (e.g., DecisionDX-UM) for individuals with primary, localized uveal melanoma.
- The test must be ordered by a specialist with experience in treating uveal melanoma.

Exclusions

- Gene expression profiling for uveal melanoma that does not meet the above criteria

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81552 81599 84999

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

UVEAL MELANOMA

Clinical Context and Test Purpose

The purpose of 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.

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 retrospective study (2016) 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% confidence interval [CI], 44% to 97%) and 100% (95% CI, 99% to 100%), respectively.(11)

Identifying patients at low-risk for metastatic disease might assist in selecting patients who could safely reduce frequency or intensity of surveillance, which could lead to improved outcomes through reduced burden.

The following PICOs were used to select literature to inform this review.

Populations
The relevant population of interest is individuals with localized uveal melanoma.

Uveal melanomas may present with visual symptoms or be detected incidentally. The diagnosis is based on funduscopic examination and other noninvasive tests, such as ultrasound and fluorescein angiography. A biopsy may be useful to collect additional information about the molecular characteristics of the tumor. Treatment of primary, localized uveal melanoma can be by surgery or radiotherapy. While treatment is effective at preventing local recurrence, patients are at risk for distant metastases for many years. Approximately 50% of patients will develop distant metastasis, which is the leading cause of death in patients with uveal melanoma.

Interventions
The test being considered is DecisionDx-UM.

DecisionDx-UM is a gene expression profile (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 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 IA, class IB, and class II phenotypes:

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

Comparators
National Comprehensive Cancer Network guidelines for uveal melanoma address the prognosis and management of uveal melanoma, stating that biopsy of the primary tumor for

molecular/chromosomal testing for prognostication is preferred over cytology alone and that the risk/benefits of biopsy for prognostic analysis for risk stratification should be carefully considered and discussed with the patient. Risk stratification to determine the frequency of follow-up should be based on the highest risk factor present.(12) Melanoma Focus (2015), a British medical nonprofit that focuses on melanoma research, published guidelines on uveal melanoma that state that prognostication and risk prediction should be based clinical, morphologic, and genetic cancer features.(13)

Outcomes

The potential beneficial outcome associated with selecting high-risk individuals for adjuvant treatment and more intensive surveillance for metastatic disease is improved survival while potential harmful outcomes are related to adverse events of treatment and increased burden of surveillance.

The potential beneficial outcome associated with selecting low-risk individuals for less intensive surveillance for metastatic disease is reduced burden; potential harmful outcomes are related to delayed detection of metastasis.

Distant metastasis can develop years or even decades after local treatment of uveal melanoma.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Study Selection Criteria

For the evaluation of clinical validity of the DecisionDx-UM test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology by score or risk category
- Included a validation cohort of patient/samples independent of the developmental cohort
- Included a suitable reference standard (outcome of metastasis or melanoma mortality)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Review of Evidence

Observational studies have reported data on the association of GEP score and clinical outcomes; they are summarized in Table 1. All studies showed strong and positive associations between GEP classification and clinical outcomes. Recent studies indicate prognostication using GEP in conjunction with other risk indicators, such as tumor stage and size, may have improved predictive capacity over GEP alone.

The first study was published by Onken et al (2012).(14) 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 II (high risk of metastasis). A total of 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 I in 276 (61.9%) cases and class II 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 I cases and 44 (25.9%) of class II 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 two years (NRI=0.37, P=0.008) and three years (NRI=0.43, P=0.001).

Two other studies reporting data on clinical validity were published in 2016.(15,16) Walter et al evaluated two cohorts of patients at two clinical centers who underwent resection for uveal melanoma.(15) This study had similar methodology to Onken (2012).(14) 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 I (61.4%) in 148 patients and class II (38.6%) in 93 patients. Again, GEP results were most strongly associated with progression-free survival.

Similar outcomes were reported by Demirci et al (2018) in a retrospective review of 293 patients with choroidal melanoma.(17) Class 2 tumors with largest basal diameter ≥ 12 mm and class 2 and 1B tumors with American Joint Committee on Cancer (AJCC) stage III showed significantly worse prognosis. At a median follow-up of 26 months, the probability of metastasis-free survival was lowest in patients with class 2 tumors (HR 0.60; 95% CI, 0.44 to 0.72) compared to patients with class 1A (HR 0.99; 95% CI, 0.94 to 0.99) or class 1B (HR 0.90; 95% CI, 0.77 to 0.96) tumors. Recent studies indicate prognostication using GEP in conjunction with other risk indicators, such as tumor stage and size, may have improved predictive capacity over GEP alone.(18)

Decatur et al (2016) was a smaller, retrospective study of 81 patients who had tumor samples available from resections occurring between 1998 and 2014.(16) GEP was class I in 35 (43%) patients, class II in 42 (52%) patients, and unknown in 4 (5%) patients. GEP class II was strongly associated with *BAP1* variants (r=0.70; p<0.001). On Cox proportional hazards analysis, GEP class II was the strongest predictor of metastases and melanoma mortality (see Table 1).

Cai et al (2018) retrospectively evaluated a cohort of 240 patients with uveal melanoma arising from the choroid and/or ciliary body.(19) The study sought to determine whether the prognostic accuracy of combined GEP and PRAME (preferentially expressed antigen in melanoma) status was noninferior to the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system for uveal melanoma. Patients were followed for a median duration of 29 months with metastasis as the primary endpoint (see Table 1). GEP class was the most significant predictor of metastasis ($P = 1.5 \times 10^{-8}$). The prognostic accuracy of an optimized GEP/PRAME model ($P = 8.6 \times 10^{-14}$) was superior to an optimized TNM model ($P = 1.3 \times 10^{-5}$).

Davanzo et al (2019) conducted a retrospective review of 107 consecutive uveal melanoma patients, including 39, 31, and 37 patients with unknown, low-, and high-risk GEP results.(20) Low-risk patients were followed with hepatic ultrasonography every 6 months, whereas high-risk patients were managed with more frequent hepatic imaging. High-risk patients (8/37) were significantly more likely to develop metastasis ($P < 0.001$) compared to patients in the low/unknown risk group (0/70) (see Table 1).

Roelofs et al (2022) performed a retrospective analysis of 343 patients with uveal melanoma who underwent GEP classification, including 255 patients with class 1 and 88 patients with class 2 results.(21) Patients were classified as being at low (GEP class 1 and tumor thickness <8 mm) or high risk of metastasis (GEP class 2 or tumor thickness ≥8mm); low-risk patients underwent annual surveillance abdominal ultrasound, while high-risk patients underwent alternating surveillance liver ultrasound and abdominal magnetic resonance imaging every 6 months according to institutional protocol. The mean follow-up was 40 ± 26 months. In univariate Cox proportional hazard regression, enucleation, ciliary body involvement, extraocular extension, tumor thickness, largest basal tumor diameter (as a continuous and categorical [>12mm] variable), and GEP class 2 were associated with future metastasis. Multivariate Cox proportional hazards regression indicated GEP class 2 and longest basal diameter >12mm remained independently predictive of metastasis-free survival, and stratified analysis further indicated longest basal diameter >12mm remained predictive of metastasis-free survival in both GEP class 1 and 2 tumors.

Singh et al (2022) performed a retrospective analysis of metastasis-free survival in patients with uveal melanoma, with a focused analysis comparing predicted (according to DecisionDx-UM metastasis-free survival prediction for GEP class 2 [i.e., 50% at 3 years, 28% at 5 years]), observed (via analysis of a cohort of consecutive patients with uveal melanoma treated at the authors' 2 institutions), and published (via a meta-analysis of patients with uveal melanoma from 7 retrospective or prospective studies utilizing GEP published between 2012 and 2021) metastasis-free survival in GEP class 2 subgroups.(22) The overall retrospective cohort consisted of 343 patients, of whom 121 were GEP class 2, while the meta-analysis pooled data from 667 GEP class 2 patients. In the analysis of GEP class 2 patients, both observed and meta-analysis-derived published metastasis-free survival at 3 and 5 years were longer than the corresponding DecisionDx-UM-predicted survival, with point estimate differences ranging from 12% to 19%. The predicted metastasis-free survival estimate was below the lower limit of the 95% confidence interval for both observed and published survival estimates at both time points.

Table 1. Studies of Clinical Validity

Study	Patient Populations	Rates of Metastases		Melanoma Mortality Rates	
		GEP Class I	GEP Class 2	GEP Class I	GEP Class II
Onken (2012)	459 patients with UM from 12 clinical centers	1.1%	25.9%[a]	NR	NR
Walter (2016)	Primary cohort: 339 patients 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 patients from a single center with available UM tumor samples arising from ciliary body or choroid		9.4[a,b] (3.1 to 28.5)		15.7[a,b] (3.6 to 69.1)
Demirci et al. (2018)	293 patients from 2 clinical centers with UM arising from the choroid	3.6%	26.5%	NR	NR
Cai et al. (2018)	240 patients from a single-center with UM arising from the choroid and/or ciliary body	10.2% 3.9% (*PRAME*-) 6.3% (*PRAME*+)	41.1% 19.6% (*PRAME*-) 21.4% (*PRAME*+)	NR	NR
Davanzo et al. (2019)	107 consecutive patients from a single-center with UM	0%	21.6%	NR	NR
Roelofs et al (2022)	343 patients from a single center with non-metastatic UM	4.3%	34%	NR	NR
Singh et al (2022)	• Observed survival cohort: 343 consecutive patients from 2 centers with UM, including 121 GEP class 2 patients • Published survival pooled cohort: 667 GEP class 2 patients	• Observed 3-year MFS: 93% (95% CI, 89% to 97%) • Observed 5-year MFS: 87% (95% CI, 81% to 93%)	3-year MFS: • Predicted: 50% • Observed: 67% (95% CI, 59% to 77%) • Published: 62% (95% CI, 57% to 66%) 5-year MFS: • Predicted: 28% • Observed: 47% (95% CI, 37% to 61%) • Published: 40% (95% CI, 34% to 46%)		

CI, confidence interval; GEP: gene expression profile; MFS: metastasis-free survival; NR: not reported; PRAME: preferentially expressed antigen in melanoma; UM: uveal melanoma.
[a] p<0.001.
[b] Reported as relative risk (95% confidence interval) for metastases (or melanoma mortality) in group 2 vs group 1.
[c] Predicted values according to DecisionDx-UM documentation.

Section Summary: Clinically Valid
Six published studies on clinical validity reported rates of metastases or melanoma mortality by GEP class. These studies have reported that GEP class II is a strong predictor of metastases and melanoma survival. Four studies have compared GEP class to clinicopathologic features and have reported that GEP classification is the strongest predictor of clinical outcomes.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because there are interventions studies, the preferred evidence would be from randomized controlled trials.

There is no direct evidence for 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.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The GEP test is associated with risk of metastatic disease and melanoma death. Although the three 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.

Plasseraud et al (2016) reported metastasis surveillance practices and patient outcomes using data from a prospective observational registry study of DecisionDX-UM conducted at four centers, which included 70 patients at the time of reporting.(23) 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 three to six 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 I. Over a median follow up of 2.38 years, more class II patients (36%) than class 1 patients (5%; p=0.002) experienced a metastasis. The three-year metastasis-free survival (MFS) rate was lower for class II patients (63%; 95% CI, 43% to 83%) than class I patients (100%; CI not specified; p=0.003). Most class I patients (n=30) had low-intensity surveillance and all (n=33) class II patients had high-intensity surveillance. Aaberg et al. (2020) published updated 5-year outcomes for 89 patients.(24) Of these 89 patients, 49 (55%) were class 1, of which 39 (80%) received low-intensity management. The 5-year metastasis-free survival was 90% for class 1 patients compared to 40.7% for class 2 patients ($P < 0.0001$). The 5-year melanoma specific survival was 94.3% for class 1 patients compared to 63.4% for class 2 patients ($P = 0.0007$). 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.(25) 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 three to six 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 I and 81 (42%) were class II. For patients with surveillance data available (n=88), all patients in GEP class I had low-intensity surveillance and all patients in GEP class 2 had high-intensity surveillance ($p<0.001$ vs class I).

It is likely that treating liver metastasis affects 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.

Khan et al (2022) conducted a multicenter, single-arm study of crizotinib as adjuvant therapy in adults with localized high-risk uveal melanoma (defined as GEP class 2 and longest basal tumor diameter >12mm).(26) This was the first published clinical trial of crizotinib in uveal melanoma. Patients received crizotinib 250 mg by mouth twice daily for a total of 48 weeks, beginning within 90 days of primary enucleation or radiotherapy. The primary outcome was 32-month relapse-free survival (RFS) rate; planned enrollment was 30 patients to provide 90% power to detect a 75% RFS rate at 32 months relative to a 50% RFS rate based on historical data. The analysis included a comparison of the primary outcome in the study cohort to a 2:1 propensity score-matched historical control. Among the 34 patients enrolled, the median age was 60 years, and all patients had an Eastern Cooperative Oncology Group performance status of 0 or 1. The mean relative dose intensity per cycle was 84%; 4 patients did not complete 48 weeks of treatment with crizotinib due to toxicity despite dose reduction. In 32 evaluable patients, at a median follow-up of 47.1 months, the estimated 32-month RFS rate was 50% (95% CI 23% to 67%). There was no difference in the primary outcome between the study cohort and the propensity score-matched historical control cohort, in whom the estimated 32-month RFS rate was 57% (95% CI 40% to 73%). All patients experienced at least 1 treatment-related adverse event, the most common of which were nausea, transaminase elevation, diarrhea, fatigue, and sinus bradycardia.

Section Summary: Clinically Useful

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 be a strong predictor 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 the 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. Classification into the low-risk group would permit reduction in the burden of surveillance without apparent harm. One well-designed non-randomized trial of crizotinib as adjuvant therapy in high-risk patients indicated no benefit in preventing disease relapse relative to historical control; however, this was the first clinical trial of crizotinib in patients with uveal melanoma, and the role, if any, of adjuvant treatment with agents known to have therapeutic activity in the relapsed and metastatic settings remains unknown.

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 identified (DecisionDx-UM) has published data related to its clinical validity and is the focus of this review. Six studies of clinical validity identified used the GEP score to predict

melanoma metastases and melanoma-specific survival. All three reported that GEP classification correlated strongly with metastatic disease and/or melanoma mortality. Four studies compared GEP classification with 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.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network
National Comprehensive Cancer Network (NCCN) guidelines for uveal melanoma state that if biopsy is performed, "molecular/chromosomal testing for prognostication is preferred over cytology alone." The guidelines include DecisionDx-UM classes as 1 of the factors used to risk stratify patients for systemic imaging and note that risk stratification to determine the frequency of follow-up should be based on the highest risk factor present.(12)

Melanoma Focus
Melanoma Focus (2015), a British medical nonprofit that focuses on melanoma research, published guidelines on uveal melanoma.(13) 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. A 2022 guideline update included several additional relevant statements, which are denoted with (2022).(27) The guidance for surveillance was updated in 2023; relevant statements are denoted with (2023).

Prognostic factors/tool
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
- Tumour height
- Tumour Largest [sic] basal diameter
- Ciliary body involvement
- Extraocular melanoma growth (macroscopic)

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).
- Presence of extraocular melanoma growth (size, presence or absence of encapsulation)
- Positive or negative expression of nuclear BAP1 protein in the tumour cells. (2022)

The following features should be recorded if cytology of tumour is available:
- Confirmation of melanoma cells (i.e., exclude differential diagnoses, particularly metastatic carcinoma) - immunocytology may be required for this, but is not always necessary.
- Cell type (modified Callender system), if possible. (2022)

Prognostic biopsy
There should be a fully informed discussion with all patients, explaining the role of biopsy including the benefits and risks. The discussion should include:
- Enabling prognostication and allow tailored follow-up
- Allowing recruitment into adjuvant trials
- Risks of having the biopsy
- Limitations of the investigation
- Effects of prognostication information on quality of life (2022)

The minimum dataset for uveal melanoma from the Royal College of Pathology (or national official equivalents) should be recorded in the pathology reports. [...]

The use of multifactorial prognostication models incorporating clinical, histological, immunohistochemical and genetic tumour features should be considered. (2022)

Where available the results of state-of-the-art molecular analysis should be combined with clinical features and standard anatomical and pathological staging for prognostication. (2022)

Tests for novel circulating blood-borne biomarkers should only be used within clinical trials or research programmes. (2022)

Surveillance
Ocular surveillance for tumour recurrence and any other ocular morbidity

- Patients should be offered surveillance of the eye initially every 6 months for 2 to 5 years and then annually depending on response to therapy and individual patient factors. If there is doubt over stability, then the interval between follow-ups can be reduced to allow for a period of closer follow up to either confirm or refute stability. (2023)

Liver Surveillance

- Patients should be offered a discussion with an oncologist or other appropriately trained healthcare professional to discuss the relative merits of metastatic surveillance. For patients who commence surveillance this should be coordinated through secondary care and not primary care. (2023)

- A multi-parameter prognostic model (e.g. LUMPO) should be used in discussion with uveal melanoma patients with respect to their individual metastatic risk, and value of liver surveillance during follow up. (2023)
- For patients without genetic analyses, modelling with LUMPO to estimate risk with or without monosomy 3 may inform discussion around risk of recurrence and value of imaging surveillance. (2023)
- Patients who are considered to have a less than 10% metastatic risk within a 10-year period as calculated by a multi-parameter prognostic model (e.g. LUMPO) should not be recommended for regular liver surveillance. (2023)
- The decision to start surveillance and the duration should be individualized based on factors such as co-morbidity and fitness to act on the results of scan findings. (2023)
- Standard surveillance should be for 10 years from the initial ocular diagnosis. This should be every 6 months for 5 years and then annually to 10 years. The choice of imaging modality should be discussed with the patient but should be focused on the liver. (2023)
- When available, patients with a known somatic SF3B1 mutation (not routinely tested at the time of this guidance) may benefit from extending surveillance for 15 years. (2023)
- Liver function tests are an inadequate tool for surveillance for uveal melanoma metastases and should not be part of routine surveillance. (2023)

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02376920	Five Year Registry Study to Track Clinical Application of DecisionDx-UM Assay Results and Associated Patient Outcomes (CLEAR)	2800	April 2022 (last update posted May 2022)
NCT02068586[a]	A Randomized Phase II Study of Adjuvant Sunitinib or Valproic Acid in High-Risk Patients With Uveal Melanoma	150	Dec 2023 (recruiting)
NCT03528408[a]	Phase II Single-arm Multi-center Study of Adjuvant Ipilimumab in Combination With Nivolumab in Subjects With High-risk Ocular Melanoma	52	Jun 2023
NCT05502900	Adjuvant Melatonin for Uveal Melanoma	100	Jan 2031

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

Government Regulations
National:

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

Local:

Wisconsin Physicians Service Insurance Corporation MAC - Part B 08202 - MAC B J - 08 Michigan, LCD ID: L37210, LCD Title: MolDX: Decision Dx-UM (UVEAL Melanoma), Original Effective Date: 9/16/17; Revision effective date: 6/27/24

This Medicare contractor will provide limited coverage for the DecisionDx-UM (Castle Bioscience, Inc.) test for the management of newly diagnosed uveal melanoma. This test is intended for the determination of metastatic risk, and to guide surveillance and referral to medical oncology (preferably an oncologist with expertise in melanoma) in patients who have a confirmed diagnosis of uveal melanoma (UM) and no evidence of metastatic disease.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Genetic, Molecular and Other Tests – Experimental/Investigational Status
Genetic Testing for Familial Cutaneous Malignant Melanoma *(CDKN2A)*

References

1. Spagnolo F, Caltabiano G, Queirolo P. Uveal melanoma. Cancer Treat Rev. Aug 2012;38(5):549-553. PMID 22270078
2. Hawkins BS. Collaborative ocular melanoma study randomized trial of I-125 brachytherapy. *Clin Trials.* Oct 2011;8(5):661-673. PMID 22013172
3. Finger RL. Intraocular melanoma. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. Cancer: Principles & Practice of Oncology. 10th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2014:1770-1779.
4. Pereira PR, Odashiro AN, Lim LA, et al. Current and emerging treatment options for uveal melanoma. Clin Ophthalmol. 2013;7:1669-1682. PMID 24003303
5. Francis JH, Patel SP, Gombos DS, et al. Surveillance options for patients with uveal melanoma following definitive management. *Am Soc Clin Oncol Educ Book.* 2013:382-387. PMID 23714555
6. Diener-West M, Reynolds SM, Agugliaro DJ, et al. Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: Collaborative Ocular Melanoma Study Group Report No. 26. *Arch Ophthalmol.* Dec 2005;123(12):1639-1643. PMID 16344433
7. Correa ZM. Assessing prognosis in uveal melanoma. *Cancer Control.* Apr 2016;23(2):93-98. PMID 27218785
8. Finger PT, AJCC-UICC Ophthalmic Oncology Task Force. The 7th edition AJCC staging system for eye cancer: an international language for ophthalmic oncology. *Arch Pathol Lab Med.* Aug 2009;133(8):1197-1198. PMID 19653708
9. Simpson E, Gallie BL, Saakyan S, et al. International Validation of the American Joint Committee on Cancer's 7th Edition Classification of Uveal Melanoma. JAMA Ophthalmol. Apr 2015; 133(4): 376-83. PMID 25555246

10. Prescher G, Bornfeld N, Hirche H, Horsthemke B, Jockel KH, Becher R. Prognostic implications of monosomy 3 in uveal melanoma. Lancet. May 4 1996;347(9010):1222-1225. PMID 8622452
11. van de Nes JA, Nelles J, Kreis S, et al. Comparing the prognostic value of BAP1 mutation pattern, chromosome 3 status, and BAP1 immunohistochemistry in uveal melanoma. *Am J* Surg Pathol. Jun 2016;40(6):796-805. PMID 27015033
12. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Melanoma. Version 1.2024; https://www.nccn.org/professionals/physician_gls/pdf/uveal.pdf. Accessed August 1, 2024
13. Nathan P, Cohen V, Coupland S, et al. Uveal Melanoma UK National Guidelines. *Eur J Cancer*. Nov 2015; 51(16):2404-12. PMID 26278648
14. Onken MD, Worley LA, Char DH, et al. Collaborative Ocular Oncology Group report number 1: prospective validation of a multi-gene prognostic assay in uveal melanoma. Ophthalmology. Aug 2012;119(8):1596-1603. PMID 22521086
15. Walter SD, Chao DL, Feuer W, et al. Prognostic Implications of Tumor Diameter in Association With Gene Expression Profile for Uveal Melanoma. *JAMA Ophthalmol.* Apr 28 2016. PMID 27123792
16. Decatur CL, Ong E, Garg N, et al. Driver Mutations in Uveal Melanoma: Associations With Gene Expression Profile and Patient Outcomes. *JAMA Ophthalmol.* Apr 28 2016. PMID 27123562
17. Demirci H, Niziol LM, Ozkurt Z, et al. Do Largest Basal Tumor Diameter and the American Joint Committee on Cancer's Cancer Staging Influence Prognostication by Gene Expression Profiling in Choroidal Melanoma. Am J Ophthalmol. Nov 2018; 195: 83-92. PMID 30081017
18. Stacey AW, Dedania VS, Materin M, et al. Improved Prognostic Precision in Uveal Melanoma through a Combined Score of Clinical Stage and Molecular Prognostication. Ocul Oncol Pathol. Feb 2022; 8(1): 35-41. PMID 35356606
19. Cai L, Paez-Escamilla M, Walter SD, et al. Gene Expression Profiling and PRAME Status Versus Tumor-Node-Metastasis Staging for Prognostication in Uveal Melanoma. Am J Ophthalmol. Nov 2018; 195: 154-160. PMID 30092184
20. Davanzo JM, Binkley EM, Bena JF, et al. Risk-stratified systemic surveillance in uveal melanoma. Br J Ophthalmol. Dec 2019; 103(12): 1868-1871. PMID 30705044
21. Roelofs KA, Grewal P, Lapere S, et al. Optimising prediction of early metastasis-free survival in uveal melanoma using a four-category model incorporating gene expression profile and tumour size. Br J Ophthalmol. May 2022; 106(5): 724-730. PMID 33589435
22. Singh AD, Binkley EM, Wrenn JM, et al. Predicted vs Observed Metastasis-Free Survival in Individuals With Uveal Melanoma. JAMA Ophthalmol. Sep 01 2022; 140(9): 847-854. PMID 35862032
23. Plasseraud KM, Cook RW, Tsai T, et al. Clinical Performance and Management Outcomes with the DecisionDx-UM Gene Expression Profile Test in a Prospective Multicenter Study. *J Oncol.* 2016;2016:5325762. PMID 27446211
24. Aaberg TM, Covington KR, Tsai T, et al. Gene Expression Profiling in Uveal Melanoma: Five-Year Prospective Outcomes and Meta-Analysis. Ocul Oncol Pathol. Oct 2020; 6(5): 360-367. PMID 33123530
25. Aaberg TM, Cook RW, Oelschlager K, et al. Current clinical practice: differential management of uveal melanoma in the era of molecular tumor analyses. Clin Ophthalmol. 2014; 8: 2449-60. PMID 25587217
26. Khan S, Lutzky J, Shoushtari AN, et al. Adjuvant crizotinib in high-risk uveal melanoma following definitive therapy. Front Oncol. 2022; 12: 976837. PMID 36106113

27. Melanoma Focus. Uveal Melanoma Guideline. n.d.; https://melanomafocus.org/activities/um-guidelines-project/. Accessed December 19, 2022.
28. Centers for Medicare and Medicaid. Wisconsin Physicians Service Insurance Corporation MAC - Part B 08202 - MAC B J - 08 Michigan, LCD ID: L37210, LCD Title: MolDX: Decision Dx-UM (Uveal Melanoma), Original effective date 9/16/17. https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?lcdid=37210&ver=15&keyword=uveal%20melanoma&keywordType=starts&areaId=s27&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=AAAAAAQAAAAA&KeyWordLookUp=Doc&KeyWordSearchType=Exact. Accessed August 1, 2024.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through August 2, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/15	6/16/15	7/16/15	Joint policy established
9/1/16	6/21/16	6/21/16	Routine review
5/1/17	3/8/17	3/4/17	Policy position change from experimental/investigational to established. Added cutaneous melanoma as investigational.
5/1/18	2/20/18	2/20/18	• Routine maintenance • Added WPS Medicare LCD
5/1/19	2/19/19		Routine maintenance
1/1/20	10/15/19		Routine maintenance
1/1/21	10/20/20		• Routine maintenance • Code update - 0081U changed to 81552 per AMA update
1/1/22	10/19/21		• Routine maintenance • Cutaneous melanoma exclusion removed
1/1/23	10/18/22		• Routine maintenance (slp)
1/1/24	10/17/23		• Routine maintenance (slp) • Vendor managed: N/A
1/1/25	10/15/24		• Routine maintenance (slp) • Vendor managed: N/A

Next Review Date: 4th Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING - GENE EXPRESSION PROFILING FOR UVEAL MELANOMA

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.