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Medical Policy

BlueCross BlueShield Kansas
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Title: Gene Expression Profiling for Uveal Melanoma

Professional / Institutional
Original Effective Date: December 28, 2015
Latest Review/Revision Date: March 27, 2025
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Populations	Interventions	Comparators	Outcomes
Individuals: • With localized uveal melanoma	Interventions of interest are: • Gene expression profile test for uveal melanoma (DecisionDx-UM)	Comparators of interest are: • Usual risk stratification without a gene expression profile test	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Other test performance measures • Functional outcomes • Health status measures • Quality of life

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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, and gene expression profile testing is commercially available

OBJECTIVE

The objective of this evidence review is to assess whether net health outcomes are improved when gene expression profile testing is used to determine the prognosis of individuals with uveal melanoma compared to determining prognosis without gene expression profile testing

BACKGROUND

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.[1,]

Uveal melanoma, although rare, is the most common primary intraocular malignancy in adults. The 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 (RCTs) 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,]

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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 they 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 RCTs to evaluate forms of radiotherapy for choroidal melanoma for 5 to 10 years.[5,] 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.

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 the American Joint Committee on Cancer classifications, the rate of metastasis-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 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 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.[1,] 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.[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.

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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 the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the 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.

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POLICY

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

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

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review was created with searches of the PubMed database. The most recent literature update was performed through December 12, 2024.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

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.

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.

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Potential methods for metastases include magnetic resonance imaging (MRI), 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 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 PICO was 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 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.

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Comparators

The National Comprehensive Cancer Network guidelines for uveal melanoma (v1.2024) 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,] In 2015, Melanoma Focus, a British medical nonprofit that focuses on melanoma research, published guidelines on uveal melanoma that state that prognostic factors should be based on clinical, morphologic, and genetic cancer features.[13,14,]

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.

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.

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).

Review of Evidence

Observational 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. 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.

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The first study was published by Onken et al (2012).[15,] 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). 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 test 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 <.001). By univariate Cox proportional hazard analysis, factors associated with metastatic disease included advanced patient age (p=.02), ciliary body involvement (p=.03), tumor diameter (p<.001), tumor thickness (p=.006), chromosome 3 status (p<.001), and GEP class (p<.001). The GEP test was associated with a significant net reclassification index over Tumor, Node, Metastasis classification for survival at 2 years (no recent illness=0.37, p=.008) and 3 years (no recent illness=0.43, p=.001).

Two other studies reporting data on clinical validity were published in 2016.[16,17,] Walter et al (2016) evaluated 2 cohorts of patients at 2 clinical centers who underwent resection for uveal melanoma.[16,] This study had a similar methodology to Onken et al (2012).[15,]The primary cohort included 339 patients, of which 132 patients were also included in the Onken et al (2012) study, 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.

Similar outcomes were reported by Demirci et al (2018) in a retrospective review of 293 patients with choroidal melanoma.[18,] 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 (Hazard Ratio [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. The authors subsequently analyzed a scoring system combining AJCC stage and GEP in the same dataset (including 3 additional patients since the 2018 publication), with results indicating better estimate of prognosis with the combined score than with use of AJCC stage or GEP alone.[19,]

Decatur et al (2016) was a smaller, retrospective study of 81 patients who had tumor samples available from resections occurring between 1998 and 2014.[17,] 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<.001). On Cox proportional hazards analysis, GEP class 2 was the strongest predictor of metastases and melanoma mortality (see Table 1).

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Cai et al (2018) retrospectively evaluated a cohort of 240 patients with uveal melanoma arising from the choroid and/or ciliary body.[20,] The study sought to determine whether the prognostic accuracy of combined GEP and *PRAME* (preferentially expressed antigen in melanoma) status was noninferior to the 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.[21,] 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 ($p<.001$) 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.[22,] 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.[23,] 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%.

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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 1	***GEP Class 2***	***GEP Class 1***	***GEP Class 2***
Onken et al (2012)[15,]	459 patients with UM from 12 clinical centers	1.1%	25.9%[a]	NR	NR
Walter et al (2016)[16,]	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 et al (2016)[17,]	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)[18,]	293 patients from 2 clinical centers with UM arising from the choroid	3.6%	26.5%	NR	NR
Cai et al (2018)[20,]	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)[21,]	107 consecutive patients from a single center with UM	0%	21.6%	NR	NR
Roelofs et al (2022)[22,]	343 patients from a single center with non-metastatic UM	4.3%	34%	NR	NR
Singh et al (2022)[23,]	• 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%	3-year MFS: • Predicted:[c] 50% • Observed: 67% (95% CI, 59% to 77%) • Published: 62% (95% CI, 57% to 66%)	NR	NR

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Study	Patient Populations	Rates of Metastases		Melanoma Mortality Rates	
		CI, 81% to 93%)	5-year MFS: • Predicted:[c] 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<.001.
[b] Reported as relative risk (95% CI) for metastases (or melanoma mortality) in group 2 versus 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 2 is a strong predictor of metastases and melanoma survival. Four studies have compared GEP class with 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, more effective therapy, 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 these are intervention studies, the preferred evidence would be from RCTs.

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.

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 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 between risk category and metastasis

and death. For a rare cancer, the studies on clinical validity include a large proportion of annual incident cases.

Plasseraud et al (2016) reported on 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.[24,]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 every 3 to 6 months and "low-intensity" surveillance was considered to be annual imaging and/or liver function testing. 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=.002) experienced a metastasis. The 3-year metastasis-free survival rate was lower for class 2 patients (63%; 95% CI, 43% to 83%) than class 1 patients (100%; CI not specified; p=.003). Most class 1 patients (n=30) had low-intensity surveillance and all (n=33) class 2 patients had high-intensity surveillance. Aaberg et al. (2020) published updated 5-year outcomes for 89 patients.[25,] 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<.0001). The 5-year melanoma-specific survival was 94.3% for class 1 patients compared to 63.4% for class 2 patients (*p*=.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 were 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.[26,] 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<.001 vs. class 1).

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).[27,] This was the first published clinical trial of crizotinib in uveal melanoma.

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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 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 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 a 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.

SUPPLEMENTAL INFORMATION
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

No review or update is scheduled on this Medical Policy. Blue Cross and Blue Shield of Kansas will continue to monitor published literature for any updated information. If there are questions about coverage of this service, please contact Blue Cross and Blue Shield of Kansas customer service, or your professional / institutional relations representative.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines (v1.2024 3) 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

In 2015, Melanoma Focus, 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 NICE, contained the following statements on prognosis and surveillance. A 2022 guideline update included several additional relevant statements, which are denoted with (2022).[14,] The guidance for surveillance was updated in 2023; relevant statements are denoted with (2023).

"4.2 Genetic and molecular features (2022)

Prognostic factors/tool

28. 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)

29. 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)

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Prognostic biopsy

30. 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)

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

32. Use the most up-to-date edition of the Tumor Node Metastasis staging system for prognostication and include in pathology/clinical reports. (2022)

33. Collect 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. (2022)

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

35. 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)

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

[...]

4.4 Surveillance

Ocular surveillance for tumour recurrence and any other ocular morbidity

40. 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

45. 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 co-ordinated through secondary care and not primary care. (2023)

46. 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)

47. 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)

48. 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)

50. 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)

51. 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)

52. 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)

57. 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			
NCT02068586[a]	A Randomized Phase ll Study of Adjuvant Sunitinib or Valproic Acid in High-Risk Patients With Uveal Melanoma	150	Dec 2025

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NCT No.	Trial Name	Planned Enrollment	Completion Date
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.

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CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
81552	Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis

REVISIONS	
12-28-2015	Policy added to the bcbsks.com web site on 11-24-2015; effective date 12-28-2015.
08-17-2016	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Updated coding bullet.
	Updated References section.
03-15-2017	Updated Description section.
	In Policy section: ▪ Added new Item A, "Gene expression profiling for uveal melanoma with DecisionDx-UM is considered medically necessary for patients with primary, localized uveal melanoma." ▪ Revised previous policy language by adding "that do not meet the above criteria" to read, "Gene expression profiling for uveal melanoma that do not meet the above criteria is considered experimental / investigational", and is now Item B.
	Updated Rationale section.
	In Coding section: ▪ Added ICD-10 codes.
	Updated References section.
	Removed Appendix section.
03-28-2018	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Updated coding bullets.
	Updated References section.
01-01-2019	In Coding section:

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REVISIONS	
	▪ Added new HCPCS code: 0081U. ▪ Removed coding bullet.
	Updated References section.
03-27-2019	Updated Rationale section.
	Updated References section.
01-01-2020	In Coding section: ▪ Added CPT Code: 81552 ▪ Deleted PLA Code: 0081U
03-23-2021	Updated Description Section.
	Updated Rationale Section.
	Updated References Section.
05-09-2022	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Converted ICD-10 codes to ranges ▪ Added: ICD-10 codes C69.90-C69.92 ▪ Removed: CPT codes 81599, 84999
	Updated References Section
03-28-2023	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Removed ICD-10 codes
	Updated References Section
03-26-2024	Updated Description Section
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	Updated References Section
03-27-2025	Updated Description Section
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	Updated References Section
03-27-2025	Archived

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