Gene Expression Profiling for Uveal Melanoma

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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) determines the expression of multiple genes in a tumor and has been proposed as an additional method to stratify patients into prognostic risk group to assess an individual's risk of metastasis.

The below table summarizes some commercially available tests, and this list may not be comprehensive as the market is changing rapidly and all the available tests may not be represented below:

Test Name	Test Description	Manufacturer
DecisionDx-UM	DecisionDx Uveal Melanoma (DecisionDx-UM) is a test designed to assess an individual's risk of metastasis. DecisionDx-UM measures gene expression of 15 genes present in an ocular melanoma tumor. This test is designed to assess the risk of metastasis within 5 years. DecisionDx-UM test results are reported as follows: • Class 1A – very low risk (2%) of metastasis within 5 years • Class 1B – moderate risk (21%) of metastasis within 5 years • Class 2 – high risk (72%) of metastasis within 5 years	Castle Biosciences
DecisionDx-PRAME	DecisionDx-PRAME is an optional additional test that can be run on the same tissue sample as DecisionDx-UM test. According to Castle Biosciences "Elevated expression of PRAME has been associated with an increased risk of metastasis in patients with uveal melanoma. When used in conjunction with results from DecisionDx-UM test, PRAME expression status may add further precision to the predicted risk of metastasis and help guide physicians and patients to the most appropriate follow-up care regimens."	Castle Biosciences
DecisionDx-UmSeq	The DecisionDx-UMSeq test, is a 7-gene panel that identifies the following: mutations at hotspots in GNAQ, GNA11, CYSLTR2, PLCB4, and SF3B1; mutations in exons 1-2 of EIF1AX; and all coding exon mutations in the BAP1 gene. This test uses next	Castle Biosciences

	generation sequencing (NGS) to identify somatic mutations in patients with uveal melanoma (UM) and can be ordered in addition to DecisionDx-UM using the same tissue specimen. The DecisionDx-UMSeq reports on clinically relevant mutations identified in any of the 7 gene targets. For each mutation found, the report describes any of the following: • Genomic location of the mutation • Type of mutation • Functional change that occurs because of the mutation • Frequency that the mutation was detected in the sample; and • Potential consequences of that mutation on gene function and relevant literature references	
Uveal Melanoma Prognostic Genetic Test	Genetic testing of eye tumor tissue to determine whether tumor has a high risk of metastasis. Methodology: Multiplex ligation-dependent probe amplification (MLPA); microsatellite analysis; sequencing. Sequencing of GNAQ, GNA11, SF3B1 and EIF1AX to detect frequently occurring mutations in uveal melanoma (UM) tumors.	Impact Genetics

Uveal Melanoma

The uveal tract is the middle layer of the wall of the eye and has three main parts: the choroid (a tissue layer filled with blood vessels), ciliary body (muscle tissue that changes the shape of the pupil in the lens), and the iris (the colored part of the eye). Uveal melanoma arises from the 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. Iris melanomas have the best prognosis; melanomas of the ciliary body have the worst prognosis.

Uveal melanoma, although rare, is the most common primary intraocular malignancy in adults. 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 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.

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. Metastatic disease is the leading cause of death in patients with uveal melanoma, and approximately 50% of patients will develop distant metastasis. Several 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 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 retrospective study of 3377 patients with uveal melanoma (2015), 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, and 50% for stage IIIB.

Genetic Analysis

Genetic analysis of uveal melanoma can provide prognostic information for the risk of developing metastatic disease. A study has shown 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 one study van de Nes et al. (2016), 89% of tumors with monosomy 3 had BAP1 variant, and no tumors without monosomy 3 had 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 group.

Clinical Context and Test Purpose
The purpose of using gene expression profiling testing 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 surveillance include magnetic resonance imaging (MRI), ultrasound, liver function testing (LFTs), and positron emission tomography (PET) scans.

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 improve outcomes. Adjuvant treatment for metastatic disease consists of radiotherapy, or systemic therapy, such as chemotherapy, immunotherapy, hormone therapy, biologic therapy, or targeted therapy.

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.

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

Uveal melanoma 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 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 metastases, which is the leading cause of death in patients with uveal melanoma.

Intervention
The testing being considered is gene expression profiling (GEP).

DecisionDx-UM
DecisionDx-UM test (Castle Biosciences Inc., Friendswood, TX) is a proprietary, multigene expression profiling (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 2 classes.

Based on the clinical outcomes from the prospective, 5- year multicenter Collaborative Ocular Oncology Group (COOG) study, the DecisionDx-UM test reports class 1A, class 1B, and class 2 phenotype:

- 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.

According to Castle Biosciences Inc., the DecisionDx-UM test results are used for the following:

- To develop specific monitoring or surveillance plans, including a more frequent monitoring with advanced imaging procedures for those individuals identified as having high risk of developing metastasis
- For individuals at a low risk of developing metastasis, a less intensive surveillance plan may balance the risks of radiation exposure associated with less frequent imaging
- To initiate referral to a medical oncologist for treatment planning which may include adjuvant treatment; and
- To improve life planning.

Comparators
The current National Comprehensive Cancer Network (NCCN) guideline for uveal melanoma (version 2.2022) 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.

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

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

Review of Evidence

DecisionDx-UM Assay

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).

Three studies have reported data on the association between gene expression profiling (GEP) score and clinical outcomes. All studies showed strong and positive associations between GEP classification and clinical outcomes.

In 2012, Onken et al., in a prospective multicenter study evaluated the prognostic performance of a 15 gene expression profiling (GEP) assay that assigns primary posterior uveal melanomas to prognostic subgroups: class 1 (low metastatic risk) and class 2 (high metastatic risk). 459 patients with posterior uveal melanoma were enrolled from 12 independent centers between June 2006 and November 2010. De-identified patient information was collected from each center, including patient age, gender, tumor thickness (measured by ultrasound), tumor diameter (defined as the largest basal tumor dimension measured by indirect ophthalmoscopy or ultrasound), ciliary body involvement (defined as any portion of the tumor extending anterior to the ora serrata), date tumor sample was obtained, cytopathologic cell type (predominantly spindle, mixed, epithelioid, unspecified melanoma cell type, acellular/quantity not sufficient for diagnosis, or information not available), last known patient survival status (alive with no metastasis, alive with metastasis, dead of metastatic disease, or dead of other causes), presence or absence of metastatic disease, date metastatic disease was first detected and date of death or most recent follow-up. The 7th edition Tumor Node Metastasis (TNM) clinical classification for uveal melanoma was performed using basal tumor diameter, thickness, and ciliary body involvement as described elsewhere. 224 patients were female and 235 were male. Mean age was 61.7 years (median 61.0 years). Mean tumor diameter was 12.8 mm (median 12.7 mm), and mean tumor thickness was 6.3 mm (median 5.5 mm). Ciliary body involvement was absent in 308 cases, present in 139 cases and unknown in 12 cases. Tumor samples were obtained by FNAB (fine needle aspiration biopsy) in 359 cases, post-enucleation FNAB in 92 cases, and local tumor in 8 cases. The cytopathologic diagnosis was spindle cell melanoma in 143 cases, mixed cell melanoma in 95 cases, epithelioid cell melanoma in 87 cases, unspecified melanoma cell type in 41 cases, acellular/quantity not sufficient for diagnosis is 60 cases, and sample not obtained for cytopathology in 33 cases. The status of chromosome 3 was assessed by multi-SNP

assay in the first 260 cases. 34 deaths occurred, 28 (82.4%) of which were due to metastatic disease. Another 19 patients developed metastases but were still alive at the time of last follow-up. The 15 gene classification was performed at the Washington University site. The GEP assay was successful in rendering a classification in 446/459 (97.2%) cases. Among the 13 samples that failed to yield a GEP result, 5 did not adhere to study protocol (improper buffer, handling, or shipping). Of the 446 cases, 276 (61.9%) were class 1 and 170 (38.1%) were class 2. Median follow was 18 months. Metastasis was detected in 3 (1.1%) patients with class 1 tumors and 44 (25.9%) patients with class 2 tumors ($p < 0.0001$). By Kaplan-Meier analysis, GEP class 2 was more strongly associated with metastasis than any of the other prognostic factors that were analyzed, including chromosome 3 status. By univariate Cox proportional hazards analysis, factors associated with metastasis included advanced patient age (p=0.02), ciliary body involvement (p=0.03), tumor diameter (p=0.0003), tumor thickness (p=0.006), tumor cell type (p=0.04), chromosome 3 status (p=0.0002) and GEP class ($p=10^{-7}$). By multivariate Code modeling, GEP class (p=0.006) was the only variable that contributed independent prognostic information. A significant association was observed between TNM classification and metastasis (p=0.003). Chromosome 3 status did not contribute additional prognostic information that was independent of GEP (p=0.2). 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). The authors concluded the GEP assay had a high technical success rate and was the most accurate prognostic marker among all the factors analyzed. GEP provided a highly significant improvement in prognostic accuracy over clinical TNM classification and chromosome 3 status. Chromosome 3 status did not provide prognostic information that was independent of GEP.

In 2016, Walter et al., retrospective observational study performed at 2 ocular oncology referral centers (Washington University in St. Louis and Tumori Foundation at California Pacific Medical Center) to determine whether any clinicopathologic factors provide independent prognostic information that may enhance the accuracy of the GEP classification. There were 339 patients in the primary cohort and 241 patients in the validation cohort. All patients underwent tumor biopsy for GEP prognostic testing. Clinicopathologic variables included patient age and sex, tumor thickness, largest basal tumor diameter (LBD), ciliary body involvement, and pathologic cell type. Patients from the primary cohort were enrolled From November 1, 1998, to March 16, 2012; the validation cohort from November 4, 1996 to November 7, 2013. Follow-up for the primary cohort was completed August 18, 2013, and for the validation cohort December 10, 2013. Data was analyzed from November 12, 2013, to November 25, 2015. The primary outcome measure was progression free survival (PFS), defined as the interval from UM diagnosis to the detection of metastatic disease. The secondary outcome measure was overall survival, defined as the interval from UM diagnosis to death due to any cause. The primary cohort consisted of 339 patients (175 women [51.6%]; 164 men [48.4%]; mean age 61.8 years) diagnosed as having uveal melanoma (UM) arising in the ciliary body and/or choroid, 132 who were included in the initial COOG study (Onken et. al. 2012 above). The GEP prognostic test results included class 1 in 190 cases (56.0%)

and class 2 in 149 cases (44.0%). First assessed the prognostic contribution of each clinical, pathologic, and molecular feature to PFS using multivariate Cox proportional hazards analysis in the primary cohort. The most significant prognostic factor was the GEP class (exp[b] = 10.33; 95% CI, 4.30-24.84; P < .001). The only other variable that provided independent prognostic information was LBD (exp[b] = 1.13; 95% CI, 1.02-1.26; P = .02). With the use of all-cause mortality as the end point, GEP class was the only significant prognostic factor (exp[b] = 7.99; 95% CI, 3.29-19.40; P < .001). To evaluate the independent prognostic value of LBD within each GEP class, we performed univariate Cox proportional hazards analysis with PFS as the end point. Among class 1 UMs, the association of LBD with PFS was exp (b) = 1.16 (95% CI, 0.99-1.37; P = 07). Among class 2 Ums, LBD showed a modest but significant association with PFS (exp[b] = 1.13; 95% CI, 1.04-1.24; P = .005). A stepwise log-rank testing was used to determine whether a threshold LBD could be identified that best separated UMs of each GEP class into groups at lower and higher risk for metastasis. For class 1 Ums, no LBD threshold provided a significant separation of tumors with respect to metastatic risk. However, 9 of 11 class 1 Ums (82%) that metastasized had an LBD of at least 12 mm. For class 2 Ums, a significant difference in metastatic risk was observed when cases were separated based on LBD of less than 12 mm vs at least 12 mm. The mean PFS was 68.9% (95% CI, 59.3-78.4) months for class 2 UMs with an LBD of less than 12 mm vs 42.1 (95% CI, 36.4-47.8) months for class 2 UMs with an LBD of at least 12 mm (log rank test, P = 0.4). The 5 year actuarial PFS estimates were 97% (3%) for class 1 UMs with an LBD of less than 12 mm, 90% (4%) for class 1 UMs with an LBD of at least 12 mm, 90% (9%) for class 2 UMs with an LBD of less than 12 mm, and 30% (7%) for class 2 UMs with an LBD of at least 12 mm. Similar results were obtained for all-cause mortality, where the 5-year actuarial overall survival estimates were 96% (4%) for class 1 UMs with an LBD of less than 12 mm, 91% (4%) for class 1 UMs with an LBD of at least 12 mm, 100% for class 2 UMs with an LBD of less than 12 mm, and 26% (7%) for class 2 UMs with an LBD of at least 12 mm.

To determine whether this 2- term predictive model consisting of GEP class plus LBD could be applied to other patients with UM, the validation cohort was analyzed. This cohort consisted of 241 patients diagnosed with UM arising in the ciliary body and/or choroid, 132 of whom were included in the initial COOG report (Onken et. al. above). This cohort did not differ significantly from the primary cohort with respect to patient age, sex, tumor thickness, ciliary body involvement, or pathologic cell type. However, the median LBD in the primary cohort was 14.6 (mean 14.6; interquartile range 12.0-17.0) mm compared with 11.5 (mean 11.5; interquartile range 9.0-13.5) mm for the validation cohort (Mann-Whitney test, P < .001). The GEP was class 1 in 148 cases (61.4%) and class 2 in 93 cases (38.6%). As with the primary cohort, GEP classification was the factor most strongly associated with PFS (exp[b], 8.25; 95% CI, 3.79-17.94; P < .001), and LBD provided independent but modest prognostic information (exp[b], 1.19; 95% CI, 1.05-1.34; P = .005). The most significant LBD partition within each GEP class with respect to metastatic risk was LBD of less than 12 mm vs at least 12 mm. The 5- year actuarial PFS survival estimates were 100% for class 1 UMs with an LBD of less than 12 mm vs 74% (14%) for class 1 UMs with an LBD of at least 12 mm (log-rank test, P =

.07). The 5- year PFS survival estimates was 69% (14%) for class 2 UMs with an LBD of less than 12 mm vs 20% (9%) for class 2 UMs with an LBD of at least 12 mm (log-rank test, P = .004).

In the initial prospective multicenter COOG validation study (Onken et al. 2012 above), no clinicopathologic feature was found to provide prognostic information that was independent of the GEP classification. In the present study, it was re-investigated whether any clinicopathologic feature may have independent prognostic value in a cohort treated by a single surgeon that included smaller tumors and longer follow-up times than were contributed by the same surgeon to the original COOG study. It was confirmed that GEP class was by far the most accurate prognostic feature and that patient age, ciliary body involvement, tumor thickness, and tumor cell type provided no prognostic information that was independent of GEP class. However, in class 2 UMs, LBD (largest basal diameter) provided modest but significant prognostic information that was independent of GEP class and that the optimal threshold between lower and higher metastatic risk was an LBD of approximately 12 mm. A statistically significant association between LBD and outcome was not observed in class 1 UMs. A weakness of this study included the retrospective study design, which likely led to small differences in clinical tumor measurements, metastatic surveillance, follow-up intervals and other factors, as well as the relatively short follow-up, which could have preferentially underestimated the rate of metastasis in class 1 tumors. The authors concluded, we confirmed that GEP class was by far the most accurate prognostic feature and that patient age, ciliary body involvement, tumor thickness and tumor cell type provided no diagnostic information that was independent of GEP class. However, we found that in class 2 UMs, LBD provided modest but significant prognostic information that was independent of GEP class and that the optimal threshold between lower and higher metastatic risk was an LBD of approximately 12 mm. A statistically significant association between LBD and outcome was not observed for class 1 UMs. These findings have important implications for patient counseling, primary tumor treatment, clinical trial enrollment, metastatic surveillance and adjuvant therapy. We are planning a prospective, multicenter study to validate these findings and to determine the optional use of LBD in guiding primary tumor treatment, clinical trial inclusion criteria, and systemic adjuvant therapy.

Decatur et al. (2016) was a smaller retrospective study on patients with uveal melanoma (UM) treated by enucleation by a single ocular oncologist between November 1, 1998 and July 31, 2014. The objective of the study was to determine the associations between driver mutations, gene expression profile (GEP) classification, clinicopathologic features and patient outcomes in UM. Frequent mutations have been described in the following 5 genes in uveal melanoma: BAP1, EIF1AX, GNA11, GNAQ, and SF3B1. Understanding the prognostic significance of these mutations could facilitate their use in precision medicine. The study cohort comprised 81 participants. Their mean age was 61.5 years and 37% (30 of 81) were female. The GEP classification was class 1 in 35 of 81 (43%), class 2 in 42 of 81 (52%), and unknown in 4 of 81 (5%). BAP1 mutations were identified in 29 of 64 (45%), GNAQ mutations in 36 of 81 (44%), GNA11 mutations in 36 of 81 (44%), SF3B1 mutations in 19 of 81 (24%) and EIF1AX mutations in 14 of 81 (17%).

Sixteen of the mutations in BAP1 and 6 of the mutations in EIF1AX were previously unreported in UM. GNAQ and GNA11 mutations were mutually exclusive. BAP1, SF3B1, and EIF1AX mutations were almost mutually exclusive with each other. Using multiple regression analysis, BAP1 mutations were associated with class 2 GEP and older patient. EIF1AX mutations were associated with class 1 GEP and the absence of ciliary body involvement. SF3B1 mutations were associated with younger patient age. GNAQ mutations were associated with the absence of ciliary body involvement and greater largest basal diameter (LBD). GNA11 mutations were not associated with any of the analyzed features. Using Cox proportional hazards modeling, class 2 GEP was the prognostic factor most strongly associated with metastasis (relative risk 9.4; 95% CI, 3.1-28.5) and melanoma-specific mortality (relative risk 15.7; 95% CI, 3.6-69.1) ($P < .001$ for both). After excluding GEP class, the presence of BAP1 mutations was the factor most strongly associated with metastasis (relative risk, 10.6; 95% CI, 3.4-33.5) and melanoma-specific mortality (relative risk 9.0; 95% CI 2.8-29.2) ($P < .001$ for both). A limitation of this study was that it included only UMs treated by enucleation, which was a matter of necessity to obtain adequate amounts of tumor tissue for the various molecular analyses that were performed. As such, the findings of the study and others that are limited to enucleation specimens may not be representative of smaller UMs that are treated by globe-sparring procedures. The authors concluded, consistent with previous work, class 2 GEP demonstrated prognostic accuracy that was superior to all other variables that were examined. After excluding GEP class, the next most accurate prognostic factor was the presence of BAP1 mutations for both time to metastasis and to melanoma-specific mortality. These findings suggest that mutational analysis of BAP1 may have value as a biomarker for poor prognosis, whereas EIF1AX and SF3B1 may be useful markers of good prognosis. These mutations may have value as prognostic markers in uveal melanoma (UM).

Cai et. al. (2018) retrospectively evaluated a cohort of 240 patients with uveal melanoma arising from the choroid and/or ciliary body. 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. 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. 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).

Section Summary
Six 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. 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 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.

There is no direct evidence that the 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.

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

The gene expression profiling (GEP) test is associated with risk of metastatic disease and melanoma death. Although the three available studies reporting on clinical validity do not specifically report on rates of survival or metastatic 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 population of annual incident cases.

Aaberg et al. (2014) reported on changes in management associated with GEP (gene expression profiling) risk classification. They analyzed Medicare claims data submitted to Castle BioSciences by 37 ocular oncologists in the United States. Data was 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. There were 191 evaluable patients, 88 (46%) had evaluable tests and adequate information on follow-up surveillance, 36 (19%) 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 were treated with low intensity surveillance and all patients in GEP class 2 were treated with high intensity surveillance ($P < 0.0001$ versus class 1). For patients with referral data (n=36), all 23 class 2 patients were referred to medical oncology; however, none of the 13 class 1 patients were referred ($P < 0.0001$ versus class 1). For patients with adjunctive treatment data only class 2 patients were recommended for adjunctive treatment regimens. The authors concluded, overall, the data in this report support the conclusion that molecular analysis, including GEP (gene expression profiling) and chromosomal analysis have been widely accepted and adopted for uveal melanoma treatment decisions. In addition to the impact on surveillance and referral management,

such information is likely to be required for entry into future clinical trials involving adjuvant therapy at major medical center. The authors recognize that there is no strong data suggesting that more intensive surveillance improves survival outcomes.

Plasseraud 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 and 33 (47%) were class 2. Over a median follow-up of 2.38 years, more class 2 patients (36%) than class 1 patients (5%; p=0.002) experienced 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. 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 outcomes were pre-specified or how data was collected, making the risk of bias high.

In 2016, Weis et al. developed a consensus- based guideline to inform practitioners on the management of uveal melanoma. Eighty- four publications, including five existing guidelines formed the evidence base. Consensus discussions by a group of content experts from medical, radiation, and surgical oncology were used to formulate the recommendations. Key recommendations highlight that, for uveal melanoma and its indeterminate melanocyte lesions in the uveal tract, management is complex and requires experienced specialists with training in ophthalmologic oncology. Staging examinations include serum and radiologic investigations. Large lesions are still most often treated with enucleation, and yet radiotherapy is the most common treatment for tumors that qualify. Adjuvant therapy has yet to demonstrate efficacy in reducing the risk of metastasis, and no systemic therapy clearly improves outcomes in metastatic disease. Where available, enrollment in clinical trials is encouraged for patients with metastatic disease. Highly selected patients might benefit from surgical resection of liver metastases.

Section Summary
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 influences 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 non-metastasized uveal melanoma have been shown to reduce the risk of metastasis.

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 gene expression profiling (GEP) testing for management decisions improves the net health outcome of patients with uveal melanoma. GEP classification appears to be strong predictor of metastatic disease and melanoma death. Aaberg et. al. (2014) has 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 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 gene expression profiling (GEP) test for uveal melanoma DecisionDx-UM, the evidence includes cross-sectional studies of assay validation and clinical validity. Six studies of clinical validity identified used the gene expression profiling (GEP) score to predict melanoma metastases and melanoma-specific survival. All six reported that GEP classification correlated strongly with metastatic disease and 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 to be a strong predictor of metastatic disease and melanoma death. There are no studies directly showing clinical utility. Absent direct evidence, a chain of evidence can be constructed to determine whether using the result of GEP testing for management decisions improves the net health outcome of patients with uveal melanoma. Aaberg et. al. (2014) has 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 a reduction in the burden of surveillance without apparent harm. Based on the review of the available peer-reviewed published literature, the DecisionDx-UM 15-gene assay has sufficient evidence for use as a prognostic test in patients diagnosed with primary, localized uveal melanoma to assist clinicians with predicting disease severity and improving disease management strategies. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Add-On Tests to the DecisionDx-UM Assay

DecisionDx-PRAME
DecisionDx-PRAME (Castle Biosciences) is an optional additional test that can be run on the same tissue sample as DecisionDx-UM assay.

According to Castle Biosciences "Elevated expression of PRAME has been associated with an increased risk of metastasis in patients with uveal melanoma (UM). When used in conjunction with results from DecisionDx-UM test, PRAME expression status may add further precision to the predicted risk of metastasis and help guide physicians and patients to the most appropriate follow-up care regimens."

DecisionDx-UMSeq Test
DecisionDxc-UMSeq Test (Castle Biosciences) is a 7-gene panel that identifies the following: mutations at hotspots in GNAQ, GNA11, CYSLTR2, PLCB4, and SF3B1; mutations in exons 1-2 of EIF1AX; and all coding exon mutations in the BAP1 gene. This test uses next generation sequencing (NGS) to identify somatic mutations in patients with uveal melanoma (UM) and can be ordered in addition to DecisionDx-UM assay using the same tissue specimen.

The DecisionDx-UMSeq reports on clinically relevant mutations identified in any of the 7 gene targets. For each mutation found, the report describes any of the following:

- Genomic location of the mutation
- Type of mutation
- Functional change that occurs because of the mutation
- Frequency that the mutation was detected in the sample; and
- Potential consequences of that mutation on gene function and relevant literature references

Summary of Evidence
There is currently insufficient evidence from two analytical validity studies (Field et.al. PRAME as an Independent Biomarker for Metastasis in Uveal Melanoma, Clinical Care Research 2016; Field et. al. Epigenetic Reprogramming and Aberrant Expression of PRAME are Associated with Increased Metastatic Risk in Class 1 and Class 2 Uveal Melanomas, Oncotarget 2016). At this time no clinical validity or clinical utility studies were identified. Per the manufacturer's website Castle Biosciences, "Additional studies of the relationship between and PRAME and uveal melanoma patient tumors are underway, including a prospective, multi-center study." Currently there is no evidence evaluating use of DecisionDx-UmSeq. As a result, no conclusions can be drawn regarding the value and usefulness of these two additional tests that can be added on to the DecisionDx-UM assay. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Uveal Melanoma Prognostic Genetic Test
Uveal Melanoma Prognostic Genetic Test (Impact Genetics) using tumor sample is used to detect specific genetic abnormalities (GNAQ, GNA11, SF3B1 and EIF1AX) in eye tumor cells (isodisomy, monosomy and trisomy); which can indicate the chance that the cancer will spread to other parts of the body.

Summary of Evidence
Currently there is no evidence evaluating the use of Uveal Melanoma Prognostic Genetic Test. As a result, no conclusions can be drawn regarding the value and usefulness of this test. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Practice Guidelines and Position Statements

Melanoma Focus
In 2022, Melanoma Focus, a British medical nonprofit that focuses on melanoma research, updated their 2015 guideline on uveal melanoma. These guidelines, which were created using a process accredited by NICE, contained the following:

- Genetic tumor biomarkers are quite distinctive in UM and enable stratification of patients into metastatic risk subgroups.

Recommendations

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:

- Patient age
- Patient sex
- Tumor location
- Tumor height
- Tumor Largest basal diameter
- Ciliary body involvement
- Extraocular melanoma growth (macroscopic and microscopic)

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 stained sections)
- Presence of extravascular matrix patterns (particularly ‘closed loops’).
- Presence of extraocular melanoma growth (size in mm; presence/absence of encapsulation; relation to surgical margin).
- Positive or negative expression of nuclear BAP1 protein in the tumor cells.

29.The following features should be recorded if cytology of tumor 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.

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

31.The minimum dataset for UM 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 TNM staging system for prognostication and include in pathology/clinical reports.

33. Collect molecular genetic and/or cytogenetic data for research and prognostication purposes where tumor material is available and where patient consent has been obtained as part of an ethically approved research program.

34. The use of multifactorial prognostication models incorporating clinical, histological, immunohistochemical and genetic tumor features should be considered.

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.

36.Tests for novel circulating blood-borne biomarkers should only be used within clinical trials or research programs.

National Comprehensive Cancer Network (NCCN)

- **Melanoma: Uveal Version 2.2022**
    - Biopsy of the primary tumor does not impact outcome but may provide prognostic information that can help inform frequency of follow-up and may be needed for eligibility for clinical trials. If biopsy is performed molecular testing for prognostication (chromosome analysis or gene expression profiling [GEP]) is preferred over cytology alone. The risks/benefits for prognostic analysis should be carefully considered and discussed.

A method of using gene expression profiling (GEP) has been developed as a prognostic tool for uveal melanoma. These methods have been used to sort tumors into two classes, showing that class 2 was associated with higher risk of metastasis than class 1. Multivariate analysis has found that class 2 is associated with a 5-fold to 20-fold higher-risk of metastasis than class 1.

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

PRIOR APPROVAL

Not applicable.

POLICY

See Related Medical Policies

- 02.04.72 Gene Expression Profiling for Cutaneous Melanoma
- 02.04.41 Genetic Testing for Familial Cutaneous Malignant Melanoma

Medically Necessary
Gene expression profiling (GEP) for uveal melanoma (UM) using DecisionDx-UM is **medically necessary** for patients with primary, localized uveal melanoma and no evidence of metastatic disease.

Investigational
Gene expression profiling (GEP) for uveal melanoma (UM) using DecisionDx-UM that does not meet the above criteria is considered **investigational** as the evidence is insufficient to determine the safety and effectiveness on net health outcomes for all other indications.

Gene expression profiling (GEP) tests for uveal melanoma (UM), including but not limited to the following, as an additional method to stratify patients into prognostic risk group to assess an individual's risk of metastasis is considered **investigational** because the evidence is insufficient to determine the effects of the technology on net health outcomes:

- DecisionDx-PRAME
- DecisionDx-UMSeq
- Uveal Melanoma Prognostic Genetic Test

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 81401 Molecular pathology procedure level 2 (Includes PRAME [preferentially expressed antigen in melanoma] [e.g., melanoma], expression analysis) (*May be utilized for DecisionDx-PRAME*)
- 81479 Unlisted molecular pathology procedure (*May be utilized for DecisionDx-UMSeq or Uveal Melanoma Prognostic Genetic Test*)
- 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 of formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis (*DecisionDx-UM*)

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POLICY HISTORY

Date	Reason	Action
October 2022	Annual Review	Policy Renewed
October 2021	Annual Review	Policy Renewed
October 2020	Annual Review	Policy Revised
October 2019	Annual Review	Policy Renewed
October 2018	Annual Review	Policy Revised
May 2018	Interim Review	Policy Revised
October 2017	Annual Review	Policy Revised
August 2017	Interim Review	Policy Revised
October 2016	Annual Review	Policy Revised
December 2015		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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