^

Genetic Testing and Genetic Expression Profiling in Patients with Uveal Melanoma

Policy Number: AHS – M2071	Prior Policy Name and Number: Not applicable
Original Effective Date: June 01, 2023	Current Effective Date: February 1, 2025
Line(s) of Business: HMO; PPO; QUEST Integration; Medicare; FEP	Precertification: Required. Refer to GTM Utilization Review Matrix

I. Policy Description

Uveal melanoma develops from melanocytes in any part of the uveal tract, including the iris, ciliary body, and choroid (Diener-West et al., 2005). UM is the most common primary cancer of the eye and has a strong propensity for metastasis (Harbour & Chen, 2017). These melanomas have significant differences from cutaneous melanomas so the management of these two classes differ considerably (Albert et al., 1996; Harbour, 2022).

Gene expression assays measure the concentration of specific mRNAs being transcribed to assess the genes that are active in a particular cell or tissue. Analyses of gene expression can be clinically useful for disease classification, diagnosis, prognosis, and tailoring treatment to underlying genetic determinants of pharmacologic response (Steiling, 2023). Gene expression profiling has been proposed as a method of risk stratification for UM.

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1) For individuals with primary, localized uveal melanoma (UM), gene expression profiling for uveal melanoma (e.g., DecisionDx-UM) **MEETS COVERAGE CRITERIA**.
2) For individuals with primary, localized UM, the following genetic markers for UM **MEET COVERAGE CRITERIA**.
   a) Copy number assessment for chromosomes 3, 6, and/or 8.
   b) Sequence analysis of the following genes:
      (i) *BAP1*
      (ii) *EIF1AX*
      (iii) *PRAME*
      (iv) *SF3B1*

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

3) All other testing for uveal melanoma (e.g., Uveal Melanoma Prognostic Genetic Test, DecisionDx-PRAME, DecisionDx-UMSeq) **DOES NOT MEET COVERAGE CRITERIA**.

III. Table of Terminology

Term	Definition
aCGH	Array comparative genomic hybridization
AJCC	American Joint Committee on Cancer
ATRIP	*ATR interacting irotein*
BAP1	*BRCA1-Associated Protein 1*
BRAF	*Proto-oncogene **B-Raf** and v-Raf murine sarcoma viral oncogene homolog B*
BRCA1	***Hereditary breast and ovarian cancer-causing gene product***
CDC45	*Cell division cycle 45*
CDH1	*Cadherin 1*
CHEK1	*Checkpoint kinase 1*
CIZ1	*Cip1-interacting zinc finger protein*
CLIA '88	Clinical Laboratory Improvement Amendments Of 1988
CMS	Centers for Medicare and Medicaid Services
COMS	Collaborative Ocular Melanoma Study
CYSLTR2	*Cysteinyl leukotriene receptor 2*
DNA	**deoxyribonucleic acid**
ECM1	*Extracellular Matrix Protein 1*
EIF1AX	*Eukaryotic translation initiation factor 1A*
EIF1B	*Eukaryotic translation initiation factor 1A X-Linked*
FDA	Food and Drug Administration
FEN1	*Flap structure-specific endonuclease 1*
FISH	fluorescence in situ hybridization
FXR1	***Fragile X mental retardation syndrome-related protein 1***
GEP	Gene expression profiling
GNA11	*Guanine nucleotide-binding protein subunit alpha-11*
GNAQ	*Guanine nucleotide-binding protein G(q) subunit alpha*
HTR2B	*5-hydroxytryptamine receptor 2B*
HUS1	HUS1 Checkpoint clamp component
ID2	**Inhibitor of DNA binding 2**
JAMA	Journal of the American Medical Association
LBD	Largest basal diameter
LCAs	Local coverage articles
LCDs	Local coverage determinations
LDTs	Laboratory-developed Tests
LIG1	*DNA ligase 1*
LMCD1	*LIM and cysteine rich domains 1*
LTA4H	*Leukotriene A4 hydrolase*
MAPK	*Mitogen-Activated Protein Kinases*

MCM10	*Minichromosome maintenance 10 Replication Initiation Factor*
MCM2	*Minichromosome maintenance complex component 2*
MCM4	*Minichromosome maintenance complex component 4*
MCM5	*Minichromosome maintenance complex component 5*
MLH3	*MutL Homolog 3*
MLPA	Multiplex Ligation-Dependent Probe Amplification
mRNA	Messenger **Ribonucleic Acid**
MRPS21	*Mitochondrial Ribosomal Protein S21*
MSH6	*MutS homolog 6*
MTUS1	*Microtubule associated scaffold protein 1*
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
OOTF	Ophthalmic Oncology Task Force
PCNA	*Proliferating cell nuclear antigen*
PCR	**polymerase chain reaction**
PLCB4	*1-Phosphatidylinositol-4,5-bisphosphate phosphodiesterase beta-4*
POLD1	*Procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1*
POLE	*DNA polymerase epsilon catalytic subunit*
PRAME	*Preferentially Expressed Antigen in Melanoma*
RAB31	***Ras-related protein***
RBM23	*RNA binding motif protein 23*
ROBO1	*roundabout guidance receptor 1*
RRs	Relative Risks
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAP130	*Histone deacetylase complex subunit SAP130*
SATB1	*special AT-rich sequence-binding protein-1*
SF3B1	*Splicing Factor [3b] Subunit B1*
SNPs	Single nucleotide polymorphism
TNM	Tumor-Node-Metastasis
UK	United Kingdom
UM	Uveal melanoma

IV. Scientific Background

Uveal melanoma (Diener-West et al.) is the most common primary cancer in the eye, with an incidence of more than 7,000 new cases each year (Scott & Gerstenblith, 2018). The mortality rate at 15 years of diagnosis of the primary tumor is approximately 50% (Kujala et al., 2003); despite enucleation or definitive radiotherapy of the primary lesion, approximately half will develop a metastasis, and the average survival after metastasis is only 9-12 months (Carvajal et al., 2014; COMS, 2001; Diener-West et al., 2005; Kath et al., 1993; Onken et al., 2012; Rietschel et al., 2005). Tebentafusp is a United States Food and Drug Administration approved treatment for adults with advanced unresectable or metastatic uveal melanoma who are HLA-1 positive. Tebentadusp is a bispecific T cell engager targeting glycoprotein 100. The drug improved one-year overall survival rates compared to immunotherapy or chemotherapy. Currently there is no effective treatment in preventing deaths from metastatic UM (Carvajal, 2023). Novel and innovative therapeutic targets for uveal melanoma are

currently being investigated. These include liver-directed therapies, immunotherapy, and targeted-therapy on single compounds or combinational therapies (Mallone et al., 2020).

UM typically presents with visual disturbance, but may be asymptomatic (Mahendraraj et al., 2016). The diagnosis of UM is based upon fundoscopic examination by an experienced clinician, which is followed by ultrasound and/or fluorescein angiography. Biopsy is generally not indicated as the clinical diagnosis of UM has an accuracy of 99 percent (Pereira et al., 2013); however, molecular characterization of the tumor can provide important information about the risk of recurrence.

The molecular pathogenesis of UM is not completely characterized. It is not associated with the frequent BRAF mutations of cutaneous melanoma. UM has been associated with activating mutations in GNAQ or GNA11 in greater than 80 percent of primary UMs leading to activation of downstream signaling pathways, including the mitogen-activated protein kinases (MAPK) pathway (Onken et al., 2008; Shoushtari & Carvajal, 2014; Van Raamsdonk et al., 2009; Van Raamsdonk et al., 2010). Inactivating somatic mutations have been found in the BRCA1-associated protein 1 (BAP1) gene in 84 percent of metastasizing tumors, implicating loss of BAP1 in the progression of UM (Harbour et al., 2010). Germline mutations of BAP1 in approximately 5 percent of patients with UMs have been associated with larger tumors and involvement of the ciliary body (Gupta et al., 2015). Recurring mutations occurring at codon 625 of the SF3B1 gene and eukaryotic translation initiation factor 1A (EIF1AX) were associated with good prognosis (Harbour et al., 2013; Harbour, 2022; Martin et al., 2013). Other mutations such as PLCB4, CYSLTR2, SF3B1, and more are often observed (Carvajal, 2023).

Metastasis is common in UM. Approximately 50% of cases will have distal recurrence with the liver and lungs as the most common sites of metastasis. As many as 30% of patients with UM will die of a systemic metastasis within 5 years of diagnosis. The National Comprehensive Cancer Network (NCCN) considers BAP1, PRAME, SF3B1, and EIF1AX mutations to be associated with varying amounts of metastasis risk (NCCN, 2023). Cytogenetic changes may also confer increased metastasis risk. The most common cytogenetic changes in UM are monosomy of chromosome 3 (possibly the single strongest factor in predicting UM metastasis) and amplification of chromosome 8q; both of which are associated with poor prognosis. Other common cytogenetic alterations include amplification of chromosome 6p and loss of 1p (Amaro et al., 2017). Caines et al. (2015) organized four cytogenetic classes of prognostic risk based on multiplex ligation-dependent probe amplification (MLPA) results. From best to worst, those classes are: “(i) normal chromosomes 3 and 8q; (Larsen et al.) chromosome 3 deletion, normal chromosome 8q; (iii) normal chromosome 3, chromosome 8q gain; and (iv) chromosome 3 deletion, chromosome 8q gain” (Caines et al., 2015).

Genetic analysis of UM can provide prognostic information for the risk of developing metastatic disease (Spagnolo et al., 2012) and “currently represents the gold standard in molecular prognosis” for uveal melanoma as it has a technical failure rate of only 3% (Mallone et al., 2020). Genetic 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. Castle Biosciences offers a gene expression profile for UM, called “Decision-DX.” This test evaluates the gene expression of 15 genes, 12 as indicator genes and 3 as controls. The three control genes are MRPS21, RBM23, and SAP130, and the 12 indicators are HTR2B, ID2, MTUS1, ECM1, ROBO1, SATB1, LTA4H, EIF1B, FXR1, CDH1, LMCD1,

and RAB31 (Onken et al., 2010). The gene expression is reported in three classes of risk; class 1A with 2% chance of the cancer metastasizing over the next 5 years, class 1B with a 21% chance of metastasis, and class 2 with a 72% chance. Although the test does not change the course of treatment, it may still provide prognostic value for the patient (DecisionDX, 2019c).

Additionally, Decision-DX offers multiple tests for prognostication of UM. DecisionDX-UMSeq is a seven gene panel intended to identify somatic mutations relevant to UM. The seven genes are as follows: GNAQ, GNA11, CYSLTR2, PLCB4, SF3B1, exons 1-2 of EIF1AX, and all coding exons of BAP1. GNAQ, GNA11, CYSLTR2, and PLCB4 are involved in G-protein-coupled receptor signaling, EIF1AX is involved with translation, SF3B1 regulates transcript usage, and BAP1 is a tumor suppressor on chromosome 3. This test will report any somatic mutations found in these seven genes, as well as an overview of any mutation found (DecisionDX, 2018, 2019b). DecisionDX also offers a test focusing on the preferentially expressed antigen in melanoma (PRAME) gene (compared to three control genes). The test reports whether the user is positive or negative, along with an overview. However, DecisionDX notes that the "exact clinical implications of PRAME are still under investigation" (DecisionDX, 2017, 2019a).
Another prognostic test available for UM is Impact Genetics' multiplex ligation-dependent probe amplification (MLPA). This test performs a copy number assessment on chromosomes 1, 3, 6, and 8 to detect monosomy, disomy, and trisomy, a microsatellite analysis on chromosome 3 to detect chromosome copy loss and/or isodisomy, and sequence analysis of GNAQ, GNA11, SF3B1, and EIF1AX (Impact, 2019b). The test combines these results with clinical and histomorphological data and predicts survival percentage at 3, 5, and 10 years (Impact, 2019a).

Analytical Validity
Plasseraud et al. (2017) examined the "technical reliability and correlation of molecular class with pathologic characteristics" of DecisionDx. The authors identified samples from de-identified clinical reports over a 6-year period. They found the inter-assay concordance of 16 samples (run on 3 consecutive days) to be 100% with strongly correlated discriminant scores (r2 = .9944), inter-assay concordance of 46 samples performed in a one-year period to be 100% with an r2 of .9747 for discriminant scores, and the inter-assay concordance of 12 assays concurrently run in duplicates to be 100% with an r2 of .9934. Concordance between two sites assessing the same tumor was 100% with r2 of 0.9818. Finally, the "technical success" of 5516 samples was 96.3% (Plasseraud et al., 2017).
Cook et al. (2018) investigated the validity of the DecisionDx-Melanoma test using formalin-fixed paraffin-embedded tumor tissue to analyze 31 genes. The authors evaluated samples from de-identified data over a 3-year period. They found inter-assay concordance on 168 specimens was 99% with strongly correlated discriminant scores (r2 = 0.96). Inter-instrument concordance was 95% with a strongly correlated r2 of .99. Overall, in tests that met tumor sample requirements, the technical success rate of the test was 98% (Cook et al., 2018).

Clinical Utility and Validity
In 2010, Onken et al. (2010) developed and validated the PCR-based 15-gene GEP assay comprising 12 discriminating genes and three endogenous control genes, analyzed the technical performance of the assay. 609 samples were taken, and the authors defined an "undetectable" gene as "if its transcript was undetectable (i.e., no Ct value) after 40 qPCR cycles." A sample was said to have failed "if one or

more endogenous controls was undetectable." By this definition, only 32 samples (of the 609) were said to have failed (Onken et al., 2010).

Damato et al. (2010) performed a study using MLPA to assess the correlation of chromosome 1p, 3, 6p, 6q, 8p, and 8q abnormalities with other risk factors and/or death. The authors examined 452 patients, and the ten-year disease-specific mortality rates were as follows: "0% in 133 tumors with no chromosome 3 loss, 55% in tumors with chromosome 3 loss but no chromosome 8q gain, and 71% in 168 tumors showing combined chromosome 3 loss and 8q gain." Lack of chromosome 6p gain was also noted as a prognosticator of poor survival. The authors concluded that "these results support the use of MLPA for routine clinical prognostication" (Damato et al., 2010)

Onken et al. (2012) further evaluated the prognostic accuracy of their GEP. A total of 459 patients from 12 independent centers were examined, and tumors were as classified as "class 1" or "class 2." The authors then compared this classification to the 7th Edition clinical Tumor-Node-Metastasis (TNM) classification and chromosome 3 status (chromosome 3 was analyzed in the first 260 samples). The GEP assay was found to have correctly classified 446 of 459 samples, with 276 in class 1 and 170 in class 2. The authors also identified metastasis in 3 class 1 patients and 44 class 2 patients. GEP class was also found to have a strong independent association with metastasis than any other prognostic factor. The authors concluded that "the GEP assay had a high technical success rate and was the most accurate prognostic marker among all of the factors analyzed. The 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" (Onken et al., 2012).

Larsen et al. (2014) evaluated the prognostic factors of the MLPA test and their associations with metastasis and survival. MLPA was used to identify cytogenetic changes in 36 patients. After adjusting for factors such as gender and age, chromosome 3 loss and 8q gain were identified to be "significant prognosticators" for poor survival. Chromosome 1p loss was also associated with metastatic death. Chromosome 6p gain and chromosome 6q loss did not show any associations with survival or metastasis, but the authors speculated this to be because of low occurrence (4 each) (Larsen et al., 2014).
Correa and Augsburger (2016) conducted a prospective case series study of 299 patients to evaluate if any conventional clinical prognostic factors for metastasis from UM have prognostic value. The researchers found that GEP class was the strongest prognostic factor for metastatic death in this series. Using a two-term model including GEP class and "largest basal diameter" (LBD) led to strong, independent significance of each factor studied. The authors concluded that "both GEP and LBD of the tumor are independent prognostic factors for metastasis and metastatic death in multivariate analysis" (Correa & Augsburger, 2016).

Plasseraud et al. (2016) conducted a prospective, multicenter study "to document patient management differences and clinical outcomes associated with low-risk Class 1 and high-risk Class 2 results indicated by DecisionDx-UM testing." The initial results of the study indicated a low risk of metastasis for Class 1 patients (n = 37) compared to Class 2 patients (n = 33) (5% versus 36%, respectively). The authors found that the Class 1 patients (as determined by DecisionDx) had a 100% 3-

year metastasis-free survival compared to 63% for Class 2 patients and that Class 2 patients received "significantly higher-intensity monitoring and more oncology/clinical trial referrals compared to Class 1 patients" (Plasseraud et al., 2016).

Aaberg et al. (2014) conducted a medical record review and cross-sectional survey of ophthalmologists to assess current clinical practices for UM and the impact of molecular prognostic testing on treatment decisions. The medical records for 191 Medicare patients was evaluated, with 88 (46%) patients having documented medical treatment actions or institutional policies related to surveillance plans. Of these 88, all GEP Class 1 UM patients were treated with low-intensity surveillance, while GEP Class 2 UM patients were treated with high-intensity surveillance. Patients with high metastatic risk (monosomy 3 or GEP Class 2) underwent more frequent surveillance with hepatic imaging and liver function testing every 3–6 months. High-risk patients were considered more suitable for adjuvant treatment protocols. The authors concluded that "the majority of ophthalmologists treating UM have adopted molecular diagnostic tests for the purpose of designing risk-appropriate treatment strategies" (Aaberg et al., 2014).

Worley et al. (2007) compared the gene expression-based classifier to the standard genetic prognostic marker, monosomy 3, for predicting metastasis in 67 primary UMs. The sensitivity and specificity for the molecular classifier (84.6% and 92.9%, respectively) were superior to monosomy 3 detected by aCGH (58.3% and 85.7%, respectively) and FISH (50.0% and 72.7%, respectively). The researchers concluded that "molecular classification based on gene expression profiling of the primary tumor was superior to monosomy 3 and clinicopathologic prognostic factors for predicting metastasis in UM" (Worley et al., 2007).

Recent studies have shown that even after controlling for gene expression profile, tumor size (≥ 12 mm) is an independent predictor of metastasis at 5 years (Walter et al., 2017; Weis et al., 2016). Weis et al. (2016) also noted that no published studies indicate that patients at high risk for future metastasis (GEP class 2) benefit from adjuvant therapy in reducing metastasis rates (Nathan et al., 2015).

Cai et al. (2018) compared the prognostic accuracy of gene expression profiling (GEP, Class 1 or 2) with PRAME status and Tumor-Node-Metastasis (TNM) staging in patients with uveal melanoma. A total of 128 patients were labeled Class 1 by the GEP, and 112 patients were labeled Class 2. PRAME status was negative in 157 cases and positive in 83 cases. TNM was stage I in 26 cases, IIA in 67 cases, IIB in 50 cases, IIIA in 59 cases and IIIB in 38 cases. Metastatic disease was detected in 59 cases after median follow-up of 29 months. GEP class was found to be associated with metastasis (Cai et al., 2018). Kucherlapati (2018) examined groups of genes to identify gene correlations in UM survival. Genes with significant alteration include MCM2, MCM4, MCM5, CDC45, MCM10, CIZ1, PCNA, FEN1, LIG1, POLD1, POLE, HUS1, CHECK1, ATRIP, MLH3, and MSH6. Exon 4 skipping in CIZ1 was previously identified as an early serum biomarker in lung cancer. MLH3 was found to have splicing variations with deletions to both Exon 5 and Exon 7 (Kucherlapati, 2018).

Szalai et al. (2018) evaluated the deterministic properties of UM, including mutation rate and metastatic rate. The metastatic rate was based on patients with three mutations: BAP1, SF3B1, and

EIF1AX. The authors found that tumors with smaller thicknesses had a higher mutation rate and that tumors with only an EIF1AX mutation did not metastasize. Further, the authors identified a small peak in metastatic rate at 1 year and a large peak at 3.5 years post-treatment for BAP1 mutations, and peaks at 2-3 years and 7 years post-treatment for SF3B1 mutations (Szalai et al., 2018).
Decatur et al. (2016) evaluated the associations between GEP classification, driver mutations, and patient outcomes in UM. A total of 81 patients treated by enucleation were examined. The GEP classified 35 patients as class 1 and 42 as class 2 (4 were unknown). The authors then performed a multiple regression analysis. BAP1 mutations were associated with class 2 GEP and older patients, EIF1AX mutations were associated with class 1 GEP, and GNA11 mutations were not associated with any analyzed features. Class 2 GEP was identified as the prognostic factor most related to metastasis and melanoma-specific mortality, with relative risks (RRs) of 9.4 and 15.7 respectively. BAP1 mutations were also strongly related to metastasis, with RRs of 10.6 and 9.0 respectively (Decatur et al., 2016).

Schefler et al. (2019) examined the relationship between PRAME expression, GEP class, and clinical features in UM cases. This retrospective, multicenter chart review study included 148 patients with UM. All patients underwent GEP and PRAME mRNA expression testing. The Tumor, Node, Metastasis (TNM) staging system was used to separate patients; a total of 51 patients were stage I, 33 patients were stage IIA, 34 patients were stage IIB, 20 patients were stage IIIA, and 10 patients were stage IIIB. The authors note, “There was no association between higher TNM stage and positive PRAME status (p = 0.129). PRAME expression was found to be independent of gender, patient age, and tumor thickness. PRAME expression was statistically associated with LBD [largest basal diameter] and tumor volume. Higher GEP class was associated with higher TNM staging” (Schefler et al., 2019). Additional research is needed to clarify these results.

V. Guidelines and Recommendations

National Comprehensive Cancer Network (NCCN)

The NCCN notes that gene expression profiling of a biopsy specimen may provide prognostic information that can assist with eligibility of clinical trials or affect management. Specifically, the guidelines state, “Biopsy of the primary tumor 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/chromosomal is preferred over cytology alone” (NCCN, 2023).

The NCCN divides the “risk of distant metastasis” into three risk groups, low, medium, and high.

- The following markers are considered **low risk**: Class 1A, disomy of chromosome 3, gain of chromosome 6p, *EIF1AX* mutations, tumor stage T1 (AJCC).
- The following markers are considered **medium risk**: Class 1B, *SF3B1* mutations, tumor stage T2 and tumor stage T3 (AJCC).
- The following markers are considered **high risk**: Class 2, monosomy of chromosome 3, gain of chromosome 8q, *BAP1* mutations, *PRAME* mutations, tumor stage T4 (AJCC)(NCCN, 2023).

Regarding extraocular recurrence or metastasis, the NCCN states that results “should be confirmed histologically whenever possible or if clinically indicated. Biopsy techniques may include FNA or core. Obtain tissue for genetic analysis (screening for mutations that may be potential targets for treatment or determine eligibility for a clinical trial from either biopsy of the metastasis (preferred) or archival

material if the patient is being considered for targeted therapy. Consider broader genomic profiling if the test results might guide future decisions or eligibility for participation in a clinical trial" (NCCN, 2023).

American Joint Committee on Cancer (AJCC)
The 7th edition of the American Joint Committee on Cancer (AJCC) classification system recommends using tumor size to predict survival and has been validated internationally. The guidelines from the AJCC Ophthalmic Oncology Task Force (OOTF) note that "the OOTF recognizes that future modifications of the AJCC staging system are inevitable. Future modifications are likely to involve incorporation of a patient's genetic and molecular UM characteristics" (AJCC, 2015).
The AJCC 8th edition updates and corrections document notes that "only minor adjustments are introduced in the AJCC Cancer Staging Manual, 8th Edition" regarding UM (AJCC, 2018). The document also states, "Prognostic biopsies of conservatively treated uveal melanomas that allow analysis of their cytogenic, gene expression, and molecular genetic features are increasingly common. However, evidence for a long-term association between these characteristics and survival according to the anatomic extent of the tumor is still incomplete" (AJCC, 2018).

United Kingdom (Van Raamsdonk et al.) Uveal Melanoma Guideline Development Group
United Kingdom (Van Raamsdonk et al.) uveal melanoma guideline development group published guidelines which were accredited by the National Institute for Health and Care Excellence (NICE). These guidelines state that: "Prognostic factors of UM are multi-factorial and include clinical, morphological, immunohistochemical and genetic features. There are several different cytogenetic and molecular techniques for evaluating genetic changes in UM but there is insufficient comparative data. No evidence was found that demonstrated one technique was superior to another" (Nathan et al., 2015).

Consensus-Based Provincial Clinical Practice Guideline
In 2016, a consensus-based guideline on the management of UM was published by a group of content experts from medical, radiation, and surgical oncology fields. These guidelines state, "Two genetic tests more precisely identify patients with worse prognosis: testing for monosomy 3 and gene-expression profiling (GEP)" (Weis et al., 2016).
National Institute of Health - National Cancer Institute Guideline (NIH-NCI)
The 2022 guidelines from the NIH specifies molecular features as key prognostic indicators. These are in addition to staging algorithms from the AJCC, which they acknowledge as the current classification system to define melanoma of the uveal tract. Key prognostic indicators from the NIH guideline specifically include:

"Molecular Features

1. Chromosomal alterations
    a. Chromosome 3 status (loss or no loss; complete or partial).
    b. Chromosome 6p status (gain or no gain).
    c. Chromosome 8q status (gain or no gain).

    Indicate:

    - Technique used for assessing chromosome status may include the following:
        - Karyotyping.

- Fluorescence in situ hybridization.
- Comparative genomic hybridization.
- Loss of heterozygosity using DNA polymorphism analysis (e.g. single nucleotide polymorphism, microsatellite).
- Other.

- How specimen was obtained may include the following:
  - Enucleation.
  - Local resection.
  - Biopsy.
  - Fine-needle aspiration biopsy.
- For needle biopsies, whether cytopathologic evaluation was performed to confirm the presence of tumor cells.

2. Gene-expression profile: class 1 or class 2
   Indicate:
   - Technique used for gene-expression profiling (e.g., microarray, pathologic complete response).
   - How specimen was obtained (e.g., enucleation, local resection, biopsy, fine-needle aspiration biopsy).
   - For needle biopsies, whether cytopathologic evaluation was performed to confirm the presence of tumor cells" (NIH, 2023).

VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.
Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status.

HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VIII. Evidence-based Scientific References

Aaberg, T. M., Jr., Cook, R. W., Oelschlager, K., Maetzold, D., Rao, P. K., & Mason, J. O., 3rd. (2014). Current clinical practice: differential management of uveal melanoma in the era of molecular tumor analyses. *Clin Ophthalmol*, *8*, 2449-2460. https://doi.org/10.2147/opth.s70839

AJCC. (2015). International Validation of the American Joint Committee on Cancer's 7th Edition Classification of Uveal Melanoma. *JAMA Ophthalmol*, *133*(4), 376-383. https://doi.org/10.1001/jamaophthalmol.2014.5395

AJCC. (2018). *AJCC 8th Edition Updates and Corrections*. https://cancerstaging.org/CSE/general/Documents/Updates%20and%20Corrections%20at%203rd%20Printing.pdf

Albert, D. M., Ryan, L. M., & Borden, E. C. (1996). Metastatic ocular and cutaneous melanoma: a comparison of patient characteristics and prognosis. *Arch Ophthalmol*, *114*(1), 107-108. http://dx.doi.org/

Amaro, A., Gangemi, R., Piaggio, F., Angelini, G., Barisione, G., Ferrini, S., & Pfeffer, U. (2017). The biology of uveal melanoma. *Cancer Metastasis Rev*, *36*(1), 109-140. https://doi.org/10.1007/s10555-017-9663-3

Cai, L., Paez-Escamilla, M., Walter, S. D., Tarlan, B., Decatur, C. L., Perez, B. M., & Harbour, J. W. (2018). Gene Expression Profiling and PRAME Status Versus Tumor-Node-Metastasis Staging for Prognostication in Uveal Melanoma. *Am J Ophthalmol*. https://doi.org/10.1016/j.ajo.2018.07.045

Caines, R., Eleuteri, A., Kalirai, H., Fisher, A. C., Heimann, H., Damato, B. E., Coupland, S. E., & Taktak, A. F. (2015). Cluster analysis of multiplex ligation-dependent probe amplification data in choroidal melanoma. *Mol Vis*, *21*, 1-11.

Carvajal, R. D. (2023, April 3). *Metastatic uveal melanoma*. https://www.uptodate.com/contents/management-of-metastatic-uveal-melanoma

Carvajal, R. D., Sosman, J. A., Quevedo, J. F., Milhem, M. M., Joshua, A. M., Kudchadkar, R. R., Linette, G. P., Gajewski, T. F., Lutzky, J., Lawson, D. H., Lao, C. D., Flynn, P. J., Albertini, M. R., Sato, T., Lewis, K., Doyle, A., Ancell, K., Panageas, K. S., Bluth, M., . . . Schwartz, G. K. (2014). Effect of Selumetinib versus Chemotherapy on Progression-Free Survival in Uveal Melanoma: A Randomized Clinical Trial. *JAMA*, *311*(23), 2397-2405. https://doi.org/10.1001/jama.2014.6096

COMS. (2001). Assessment of metastatic disease status at death in 435 patients with large choroidal melanoma in the Collaborative Ocular Melanoma Study (COMS): COMS report no. 15. *Arch Ophthalmol*, *119*(5), 670-676. http://dx.doi.org/

Cook, R. W., Middlebrook, B., Wilkinson, J., Covington, K. R., Oelschlager, K., Monzon, F. A., & Stone, J. F. (2018). Analytic validity of DecisionDx-Melanoma, a gene expression profile test for determining metastatic risk in melanoma patients. *Diagn Pathol*, *13*(1), 13. https://doi.org/10.1186/s13000-018-0690-3

Correa, Z. M., & Augsburger, J. J. (2016). Independent Prognostic Significance of Gene Expression Profile Class and Largest Basal Diameter of Posterior Uveal Melanomas. *Am J Ophthalmol*, *162*, 20-27.e21. https://doi.org/10.1016/j.ajo.2015.11.019

Damato, B., Dopierala, J. A., & Coupland, S. E. (2010). Genotypic Profiling of 452 Choroidal Melanomas with Multiplex Ligation-Dependent Probe Amplification. *Clinical Cancer Research*, *16*(24), 6083. https://doi.org/10.1158/1078-0432.CCR-10-2076

Decatur, C. L., Ong, E., Garg, N., Anbunathan, H., Bowcock, A. M., Field, M. G., & Harbour, J. W. (2016). Driver Mutations in Uveal Melanoma: Associations With Gene Expression Profile and Patient Outcomes. *JAMA Ophthalmol*, *134*(7), 728-733. https://doi.org/10.1001/jamaophthalmol.2016.0903

DecisionDX. (2017). DecisionDx-PRAME Result. https://www.myuvealmelanoma.com/wp-content/uploads/2018/01/UM_PRAMEpos_Report_Template_V2.pdf

DecisionDX. (2018). DecisionDx-UMSeq Report. https://www.myuvealmelanoma.com/wp-content/uploads/2018/01/UM-NGS-Report-Sample-Final-v1-12202017.pdf

DecisionDX. (2019a). DecisionDx-PRAME Summary. https://www.myuvealmelanoma.com/health-care-professionals/decisiondx-prame-summary/

DecisionDX. (2019b). DecisionDx-UMSeq Summary. https://www.myuvealmelanoma.com/health-care-professionals/decisiondx-umseq-summary/

DecisionDX. (2019c). Overview of DecisionDx®-UM. https://www.myuvealmelanoma.com/uveal-melanoma-testing/overview-decisiondx-um/

Diener-West, M., Reynolds, S. M., Agugliaro, D. J., Caldwell, R., Cumming, K., Earle, J. D., Hawkins, B. S., Hayman, J. A., Jaiyesimi, I., Jampol, L. M., Kirkwood, J. M., Koh, W. J., Robertson, D. M., Shaw, J. M., Straatsma, B. R., & Thoma, J. (2005). Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: Collaborative Ocular Melanoma Study Group Report No. 26. *Arch Ophthalmol*, *123*(12), 1639-1643. https://doi.org/10.1001/archopht.123.12.1639

Gupta, M. P., Lane, A. M., DeAngelis, M. M., Mayne, K., Crabtree, M., Gragoudas, E. S., & Kim, I. K. (2015). Clinical Characteristics of Uveal Melanoma in Patients With Germline BAP1 Mutations. *JAMA Ophthalmol*, *133*(8), 881-887. https://doi.org/10.1001/jamaophthalmol.2015.1119

Harbour, J. W., & Chen, R. (2017). The DecisionDx-UM Gene Expression Profile Test Provides Risk Stratification and Individualized Patient Care in Uveal Melanoma. *PLOS Currents Evidence on Genomic Tests*. https://doi.org/10.1371/currents.eogt.af8ba80fc776c8f1ce8f5dc485d4a618

Harbour, J. W., Onken, M. D., Roberson, E. D., Duan, S., Cao, L., Worley, L. A., Council, M. L., Matatall, K. A., Helms, C., & Bowcock, A. M. (2010). Frequent mutation of BAP1 in metastasizing uveal melanomas. *Science*, *330*(6009), 1410-1413. https://doi.org/10.1126/science.1194472

Harbour, J. W., Roberson, E. D., Anbunathan, H., Onken, M. D., Worley, L. A., & Bowcock, A. M. (2013). Recurrent mutations at codon 625 of the splicing factor SF3B1 in uveal melanoma. *Nat Genet*, *45*(2), 133-135. https://doi.org/10.1038/ng.2523

Harbour, J. W., Shih, Helen. (2022, August 31). *Initial management of uveal and conjunctival melanomas*. https://www.uptodate.com/contents/initial-management-of-uveal-and-conjunctival-melanomas

Impact. (2019a). Benefits of our test. https://impactgenetics.com/wp-content/uploads/2019/03/UM-Patient-Brochure-11Mar2019.pdf

Impact. (2019b). Uveal Melanoma Genetic Prognostic Test. https://impactgenetics.com/testing-services/uveal-melanoma-um/

Kath, R., Hayungs, J., Bornfeld, N., Sauerwein, W., Hoffken, K., & Seeber, S. (1993). Prognosis and treatment of disseminated uveal melanoma. *Cancer*, *72*(7), 2219-2223. http://dx.doi.org/

Kucherlapati, M. (2018). Examining transcriptional changes to DNA replication and repair factors over uveal melanoma subtypes. *BMC Cancer*, *18*(1), 818. https://doi.org/10.1186/s12885-018-4705-y

Kujala, E., Makitie, T., & Kivela, T. (2003). Very long-term prognosis of patients with malignant uveal melanoma. *Invest Ophthalmol Vis Sci*, *44*(11), 4651-4659. http://dx.doi.org/

Larsen, A. C., Holst, L., Kaczkowski, B., Andersen, M. T., Manfe, V., Siersma, V. D., Kolko, M., Kiilgaard, J. F., Winther, O., Prause, J. U., Gniadecki, R., & Heegaard, S. (2014). MicroRNA expression analysis and Multiplex ligation-dependent probe amplification in metastatic and non-metastatic uveal melanoma. *Acta Ophthalmol*, *92*(6), 541-549. https://doi.org/10.1111/aos.12322

Mahendraraj, K., Lau, C. S., Lee, I., & Chamberlain, R. S. (2016). Trends in incidence, survival, and management of uveal melanoma: a population-based study of 7,516 patients from the Surveillance, Epidemiology, and End Results database (1973–2012). In *Clin Ophthalmol* (Vol. 10, pp. 2113-2119). https://doi.org/10.2147/opth.s113623

Mallone, F., Sacchetti, M., Lambiase, A., & Moramarco, A. (2020). Molecular Insights and Emerging Strategies for Treatment of Metastatic Uveal Melanoma. *Cancers*, *12*(10), 2761. https://doi.org/10.3390/cancers12102761

Martin, M., Masshofer, L., Temming, P., Rahmann, S., Metz, C., Bornfeld, N., van de Nes, J., Klein-Hitpass, L., Hinnebusch, A. G., Horsthemke, B., Lohmann, D. R., & Zeschnigk, M. (2013). Exome sequencing identifies recurrent somatic mutations in EIF1AX and SF3B1 in uveal melanoma with disomy 3. *Nat Genet*, *45*(8), 933-936. https://doi.org/10.1038/ng.2674

Nathan, P., Cohen, V., Coupland, S., Curtis, K., Damato, B., Evans, J., Fenwick, S., Kirkpatrick, L., Li, O., Marshall, E., McGuirk, K., Ottensmeier, C., Pearce, N., Salvi, S., Stedman, B., Szlosarek, P., & Turnbull, N. (2015). Uveal Melanoma UK National Guidelines. *Eur J Cancer*, *51*(16), 2404-2412. https://doi.org/10.1016/j.ejca.2015.07.013

NCCN. (2023). *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)*
Melanoma: Uveal
Version 1.2023 — May 4, 2023
https://www.nccn.org/professionals/physician_gls/pdf/uveal.pdf

NIH. (2023). Intraocular (Uveal) Melanoma Treatment (PDQ®)–Health Professional Version. Retrieved July 27, 2021, from https://www.cancer.gov/types/eye/hp/intraocular-melanoma-treatment-pdq

Onken, M. D., Worley, L. A., Char, D. H., Augsburger, J. J., Correa, Z. M., Nudleman, E., Aaberg, T. M., Jr., Altaweel, M. M., Bardenstein, D. S., Finger, P. T., Gallie, B. L., Harocopos, G. J., Hovland, P. G., McGowan, H. D., Milman, T., Mruthyunjaya, P., Simpson, E. R., Smith, M. E., Wilson, D. J., . . . Harbour, J. W. (2012). Collaborative Ocular Oncology Group report number 1: prospective validation of a multi-gene prognostic assay in uveal melanoma. *Ophthalmology*, *119*(8), 1596-1603. https://doi.org/10.1016/j.ophtha.2012.02.017

Onken, M. D., Worley, L. A., Long, M. D., Duan, S., Council, M. L., Bowcock, A. M., & Harbour, J. W. (2008). Oncogenic mutations in GNAQ occur early in uveal melanoma. *Invest Ophthalmol Vis Sci*, *49*(12), 5230-5234. https://doi.org/10.1167/iovs.08-2145

Onken, M. D., Worley, L. A., Tuscan, M. D., & Harbour, J. W. (2010). An accurate, clinically feasible multi-gene expression assay for predicting metastasis in uveal melanoma. *J Mol Diagn*, *12*(4), 461-468. https://doi.org/10.2353/jmoldx.2010.090220

Pereira, P. R., Odashiro, A. N., Lim, L. A., Miyamoto, C., Blanco, P. L., Odashiro, M., Maloney, S., De Souza, D. F., & Burnier, M. N. (2013). Current and emerging treatment options for uveal melanoma. *Clin Ophthalmol*, *7*, 1669-1682. https://doi.org/10.2147/opth.s28863

Plasseraud, K. M., Cook, R. W., Tsai, T., Shildkrot, Y., Middlebrook, B., Maetzold, D., Wilkinson, J., Stone, J., Johnson, C., Oelschlager, K., & Aaberg, T. M. (2016). Clinical Performance and Management Outcomes with the DecisionDx-UM Gene Expression Profile Test in a Prospective Multicenter Study. *J Oncol*, *2016*, 5325762. https://doi.org/10.1155/2016/5325762

Plasseraud, K. M., Wilkinson, J. K., Oelschlager, K. M., Poteet, T. M., Cook, R. W., Stone, J. F., & Monzon, F. A. (2017). Gene expression profiling in uveal melanoma: technical reliability

and correlation of molecular class with pathologic characteristics. *Diagn Pathol*, *12*(1), 59. https://doi.org/10.1186/s13000-017-0650-3

Rietschel, P., Panageas, K. S., Hanlon, C., Patel, A., Abramson, D. H., & Chapman, P. B. (2005). Variates of survival in metastatic uveal melanoma. *J Clin Oncol*, *23*(31), 8076-8080. https://doi.org/10.1200/jco.2005.02.6534

Schefler, A. C., Koca, E., Bernicker, E. H., & Correa, Z. M. (2019). Relationship between clinical features, GEP class, and PRAME expression in uveal melanoma. *Graefes Arch Clin Exp Ophthalmol*, *257*(7), 1541-1545. https://doi.org/10.1007/s00417-019-04335-w

Scott, J. F., & Gerstenblith, M. R. (2018). Noncutaneous Melanoma. In J. F. Scott & M. R. Gerstenblith (Eds.), *Noncutaneous Melanoma*. Codon Publications Copyright © 2018 Codon Publications. https://doi.org/10.15586/codon.noncutaneousmelanoma.2018

Shoushtari, A. N., & Carvajal, R. D. (2014). GNAQ and GNA11 mutations in uveal melanoma. *Melanoma Res*, *24*(6), 525-534. https://doi.org/10.1097/cmr.0000000000000121

Spagnolo, F., Caltabiano, G., & Queirolo, P. (2012). Uveal melanoma. *Cancer Treat Rev*, *38*(5), 549-553. https://doi.org/10.1016/j.ctrv.2012.01.002

Steiling, K., Christenson, Stephanie. (2023, July 13). *Tools for genetics and genomics: Gene expression profiling*. https://www.uptodate.com/contents/tools-for-genetics-and-genomics-gene-expression-profiling

Szalai, E., Jiang, Y., van Poppelen, N. M., Jager, M. J., de Klein, A., Kilic, E., & Grossniklaus, H. E. (2018). Association of Uveal Melanoma Metastatic Rate With Stochastic Mutation Rate and Type of Mutation. *JAMA Ophthalmol*. https://doi.org/10.1001/jamaophthalmol.2018.2986

Van Raamsdonk, C. D., Bezrookove, V., Green, G., Bauer, J., Gaugler, L., O'Brien, J. M., Simpson, E. M., Barsh, G. S., & Bastian, B. C. (2009). Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. *Nature*, *457*(7229), 599-602. https://doi.org/10.1038/nature07586

Van Raamsdonk, C. D., Griewank, K. G., Crosby, M. B., Garrido, M. C., Vemula, S., Wiesner, T., Obenauf, A. C., Wackernagel, W., Green, G., Bouvier, N., Sozen, M. M., Baimukanova, G., Roy, R., Heguy, A., Dolgalev, I., Khanin, R., Busam, K., Speicher, M. R., O'Brien, J., & Bastian, B. C. (2010). Mutations in GNA11 in uveal melanoma. *N Engl J Med*, *363*(23), 2191-2199. https://doi.org/10.1056/NEJMoa1000584

Walter, S., Department of Ophthalmology, B. P. E. I., University of Miami, Miami, FL, Chao, D. L., Department of Ophthalmology, U. S. o. M., San Francisco, CA, Schiffman, J. C., Department of Ophthalmology, B. P. E. I., University of Miami, Miami, FL, Feuer, W. J., Department of Ophthalmology, B. P. E. I., University of Miami, Miami, FL, Harbour, J. W., Department of Ophthalmology, B. P. E. I., University of Miami, Miami, FL, & Sylvester Comprehensive Cancer Center, U. o. M. M. S. o. M., Miami, FL. (2017). Tumor diameter contributes prognostic information that enhances the accuracy of gene expression profile molecular classification in uveal melanoma. *Invest Ophthalmol Vis Sci*, *56*(7), 4334-4334. http://iovs.arvojournals.org/article.aspx?articleid=2334273

Weis, E., Salopek, T., McKinnon, J., Larocque, M., Temple-Oberle, C., Cheng, T., McWhae, J., Sloboda, R., & Shea-Budgell, M. (2016). Management of uveal melanoma: a consensus-based provincial clinical practice guideline. *Curr Oncol*, *23*(1), e57-64. https://doi.org/10.3747/co.23.2859

Worley, L. A., Onken, M. D., Person, E., Robirds, D., Branson, J., Char, D. H., Perry, A., & Harbour, J. W. (2007). Transcriptomic versus chromosomal prognostic markers and clinical outcome in uveal melanoma. *Clin Cancer Res*, *13*(5), 1466-1471. https://doi.org/10.1158/1078-0432.ccr-06-2401

IX. Policy History

Action Date	Action
06/01/2023	Initial policy implementation
11/21/2023	Policy approved by Medical Directors
12/15/2023	Policy approved at UMC
2/01/2025	Policy effective date following notification period