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Genetic Testing and Genetic Expression Profiling in Patients with Uveal Melanoma

Policy Number: AHS – M2071 – Genetic Testing and Genetic Expression Profiling in Patients with Uveal Melanoma	Prior Policy Name and Number, as applicable: AHS-M2071-Gene Expression Profiling for Uveal Melanoma
Policy Revision Date: 12/01/2024 Initial Policy Effective Date: 12/01/2024	

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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, 2013). 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. Related Policies

Policy Number	Policy Title
AHS-M2029	Molecular Testing for Cutaneous Melanoma

III. 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" of this policy document.

1) For patients with primary, localized uveal melanoma (UM), gene expression profiling for uveal melanoma (e.g., DecisionDx-UM) **MEETS COVERAGE CRITERIA**.

2) For patients with primary, localized UM, the following genetic markers for UM **MEET COVERAGE CRITERIA** based on NCCN guidelines:

    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**.

NOTES:

Note: For 2 or more gene tests being run on the same platform, please refer to AHS-R2162 Reimbursement Policy.

IV. 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

V. 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, 2024). 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).

Uveal melanoma 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 five 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, 2024).

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 five 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 three percent (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 two percent chance of the cancer metastasizing over the next five 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, 2024c).

Additionally, Decision-DX offers multiple tests for prognostication of UM. DecisionDX-UM*Seq* 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, 2024b). 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, 2024a).

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 six year period. They found the inter-assay concordance of 16 samples (run on three consecutive days) to be 100% with strongly correlated discriminant scores (r^2 = .9944), inter-assay concordance of 46 samples performed in a one-year period to be 100% with an r^2 of .9747 for discriminant scores, and the inter-assay concordance of 12 assays concurrently run in duplicates to be 100% with an r^2 of .9934. Concordance between two sites assessing the same tumor was 100% with r^2 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 three year period. They found inter-assay concordance on 168 specimens was 99% with strongly correlated discriminant scores (r^2 = 0.96). Inter-instrument concordance was 95% with a strongly correlated r^2 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. A total of 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 three 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 (four 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% three 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 three to six 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 five 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 one year and a large peak at 3.5 years post-treatment for *BAP1* mutations, and peaks at two to three years and seven 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 (four 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.

VI. 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 2023 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:
        o Karyotyping.
        o Fluorescence in situ hybridization.
        o Comparative genomic hybridization.
        o Loss of heterozygosity using DNA polymorphism analysis (e.g. single nucleotide polymorphism, microsatellite).
        o Other.
    - How specimen was obtained may include the following:
        o Enucleation.
        o Local resection.
        o Biopsy.
        o 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).

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. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
81347	SF3B1 (splicing factor [3b] subunit B1) (eg, myelodysplastic syndrome/acute myeloid leukemia) gene analysis, common variants (eg, A672T, E622D, L833F, R625C, R625L)
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) **Gene:** *PRAME (preferentially expressed antigen in melanoma) (eg, melanoma), expression analysis*
81479	Unlisted molecular pathology procedure
81552	Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis
81599	Unlisted multianalyte assay with algorithmic analysis

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

IX. Evidence-based Scientific References

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X.   Review/Revision History

Effective Date	Summary
12/01/2024	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following changes were made for clarity and consistency: New Note was added to reflect changes to Avalon's definition of a genetic panel within R2162: "Note: For 2 or more gene tests being run on the same platform, please refer to AHS-R2162-Reimbursement Policy."
12/01/2024	Initial Policy Implementation