**Gene Expression Profiling for Uveal Melanoma**

Policy Number: **AHS – M2071** – Gene Expression Profiling for Uveal Melanoma  
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**Policy Description**

Uveal melanoma (UM) develops from melanocytes in any part of the uveal tract, including the iris, ciliary body, and choroid. UM is the most common primary cancer of the eye and has a strong propensity for metastasis (J. William Harbour & Chen, 2017). These melanomas have significant differences from cutaneous melanomas so the management of these two classes differ considerably (Albert, Ryan, & Borden, 1996; J. W. Harbour, Shih, Helen, 2018).

Gene expression assays measure the amount 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, 2019). Gene expression profiling has been proposed as a method of risk stratification for UM.

**Related Policies**

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<td>AHS-M2109</td>
<td>Molecular Panel Testing of Cancers to Identify Targeted Therapy</td>
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**Indications and/or Limitations of Coverage**

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request

1. Gene expression profiling for uveal melanoma using tests such as DecisionDx-UM is **EXPERIMENTAL AND INVESTIGATIONAL** for patients with primary, localized UM.

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

3. All other gene expression profiling tests (e.g. DecisionDx-PRAME) or genetic analysis for genetic markers not listed above (e.g. DecisionDx-UMSeq) is **EXPERIMENTAL AND INVESTIGATIONAL**.

**Scientific Background**

Uveal melanoma (UM) is the most common primary cancer in the eye, with an incidence of around 2,000 new cases each year (Egan, Seddon, Glynn, Gragoudas, & Albert, 1988; Mahendraraj, Lau, Lee, & Chamberlain, 2016). The mortality rate at 15 years of diagnosis of the primary tumor is approximately 50% (Kujala, Makitie, & Kivela, 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). Currently there is no effective treatment in preventing deaths from metastatic UM (Carvajal, 2018).

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 but 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 UM 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 *BRCA1*-associated protein 1 (*BAP1*) gene in 84 percent of metastasizing tumors, implicating loss of *BAP1* in the progression of UM (J. W. Harbour et al., 2010). Germline mutations of *BAP1* in approximately 5 percent of patients with UM 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 (J. W. Harbour et al., 2013; J. W. Harbour, Shih, Helen, 2018; Martin et al., 2013). Other mutations such as *PLCB4*, *CYSLTR2*, *SF3B1* and more are often observed (Carvajal, 2018).

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 NCCN considers *BAP1*, *PRAME*, *SF3B1*, and *EIF1AX* mutations to be associated with varying amounts of metastasis risk (NCCN, 2019). 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 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; (ii) 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, Caltabiano, & Queirolo, 2012). 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 3 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, Worley, Tuscan, & Harbour, 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 7 gene panel intended to identify somatic mutations relevant to UM. The 7 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 7 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 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 ($r^2 = .9944$), 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 .9818. Finally, the “technical success” of 5516 samples was 96.3% (Plasseraud et al., 2017).

Clinical Validity and Utility

In 2010 Onken et al 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 performed a study using the MLPA and assessing the correlation of the 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, Dopierala, & Coupland, 2010).

Onken et al further evaluated the prognostic accuracy of their GEP. 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 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 (UM) and the impact of molecular prognostic testing on treatment decisions. The medical records for 191 Medicare patients was evaluated, 88 (46%) with 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 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 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 (Weis et al., 2016) (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. 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.

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.

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. 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.

Decatur et al evaluated the associations between the gene expression profile (GEP) classification, driver mutations, and patient outcomes in UM. 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 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).

**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. Broader genomic profiling may be “considered” if test results may guide management.

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

The following genetic markers are considered low risk: Class 1A of DecisionDX’s GEP, disomy of chromosome 3, gain of chromosome 6p, and EIF1AX mutations.
The following genetic markers are considered medium risk: Class 1B of DecisionDX’s GEP and SF3B1 mutations.

The following genetic markers are considered high risk: Class 2 of DecisionDX’s GEP, monosomy of chromosome 3, gain of chromosome 8q, BAP mutations, and PRAME mutations (NCCN, 2019).

**American Joint Committee on Cancer (AJCC)**

The 7th edition of the American Joint Committee on Cancer 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).”

**National Institute for Health and Clinical Excellence (NICE) Guidelines**

NICE Guidelines (Nathan et al., 2015) state that: “Prognostic factors of UM are multi-factorial and include clinical, morphological, immunohistochemical and genetic features. There are a number of 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.”

**State and Federal Regulations, as applicable**

A search for “melanoma” on July 3, 2019, did not yield any results relevant to UM. Additionally, 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). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

**Applicable CPT/HCPCS Procedure Codes**

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<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
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<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
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<tr>
<td>0081U</td>
<td>Oncology (UM), mRNA, Gene-Expression Profiling By Real-Time RT-PCR of 15 Genes (12 Content And 3 Housekeeping Genes), Utilizing Fine Needle Aspirate Or Formalin-Fixed Paraffin-Embedded Tissue, Algorithm Reported As Risk Of Metastasis</td>
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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.

**Evidence-based Scientific References**


**Policy Implementation/Update Information**

1/1/20 New Policy

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