Corporate Medical Policy

Genetic Testing and Genetic Expression Profiling in Patients with Uveal Melanoma AHS - M2071

File Name: genetic_testing_and_genetic_expression_profiling_in_patients_with_uveal_melanoma
Origination: 1/1/2019
Last Review: 11/2022

Description of Procedure or Service

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 (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, 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:
Genetic Testing and Genetic Expression Profiling in Patients with Cutaneous Melanoma AHS-M2029

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for genetic testing and genetic expression profiling in patients with uveal melanoma when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing and Genetic Expression Profiling in Patients with Uveal Melanoma is covered

1. For patients with primary, localized uveal melanoma (UM), gene expression profiling for uveal melanoma using tests such as DecisionDx-UM is considered medically necessary.
2. For patients with primary, localized UM, the following genetic markers for UM are considered medically necessary 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. SFB1

When Genetic Testing and Genetic Expression Profiling in Patients with Uveal Melanoma is not covered

Multiplex ligation-dependent probe amplification (MLPA) tests (eg., Uveal Melanoma Prognostic Genetic Test) and all other gene expression profiling tests (e.g., DecisionDx-PRAME) or genetic analysis for genetic markers (e.g., DecisionDx-UMSeq) not listed above are considered investigational.

Policy Guidelines

Uveal melanoma (UM) is the most common primary cancer in the eye, with an incidence of around 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, 2022). 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 uveal melanoma 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 *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, 2018; Martin et al., 2013). Other mutations such as *PLCB4*, *CYSLTR2*, *SF3B1*, and more are often observed (Carvajal, 2022).

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, 2021). 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; (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 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-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, 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 (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 3-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. 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 uveal melanoma (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 (Worley et al., 2007) compared the gene expression-based classifier to the standard genetic prognostic marker, monosomy 3, for predicting metastasis in 67 primary uveal melanomas. 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, tumour 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 (Caiet al., 2018).

Kucherlapati (2018) examine small 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* (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.

State and Federal Regulations, as applicable

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.

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, 2021).

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, 2021).

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, 2021).

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).

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 (UK) Uveal Melanoma Guideline Development Group

United Kingdom (UK) 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

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, 2021)

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81347, 81401, 81479, 81552, 81599

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

For Policy Titled: Gene Expression Profiling for Uveal Melanoma

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Specialty Matched Consultant Advisory Panel 6/2019

Medical Director review 11/2019

Specialty Matched Consultant Advisory Panel 6/2020

Medical Director review 6/2020

For Policy Titled: Genetic Testing and Genetic Expression Profiling in Patients with Uveal Melanoma

Medical Director review 10/2020

Specialty Matched Consultant Advisory Panel 6/2021

Medical Director review 6/2021

Medical Director review 10/2021

Medical Director review 11/2022

Policy Implementation/Update Information

For Policy Titled: Gene Expression Profiling for Uveal Melanoma

1/1/2019 New policy developed. BCBSNC will provide coverage for gene expression profiling for uveal melanoma when it is determined to be medically necessary and criteria are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)

7/16/2019 Specialty Matched Consultant Advisory Panel review 6/19/2019. No change to policy statement. (lpr)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (hb)

11/12/19 Statement added to the When Not Covered section that testing is investigational in all other situations. (hb)

12/31/19 Reviewed by Avalon 3rd Quarter 2019 CAB. Under "When Covered" section: Added coverage indication statements for chromosomes 3, 6, 8 and sequence analysis for genes (BAP1, EIF1AX, PRAME, SF3B1). Added CPT code 81552 to Billing/Coding section for effective date 1/1/2020. Medical Director review 11/2019. (lpr)

6/30/20 Specialty Matched Consultant Advisory Panel review 6/17/2020. No change to policy statement. Medical Director review 6/2020. (lpr)

For Policy Titled: Genetic Testing and Genetic Expression Profiling in Patients with Uveal Melanoma

11/10/20 Reviewed by Avalon 3rd Quarter 2020 CAB. **Title changed from: Gene Expression Profiling for Uveal Melanoma to: Genetic Testing and Genetic Expression Profiling in Patients with Uveal Melanoma.** Literature review. Deleted CPT code 0081U and added CPT code 81401 to Billing/Coding section. Medical Director review 10/2020. (lpr)

7/13/21 Specialty Matched Consultant Advisory Panel review 6/16/2021. Medical Director review 6/2021. No change to policy statement. (lpr)

11/16/21 Reviewed by Avalon 3rd Quarter 2021 CAB. Updated policy description, policy guidelines, references. Added MLPA test to investigational for all other situations statement under When Not Covered. Added related policy section. Added CPT 81347 to Billing/Coding section. Medical Director review 10/2021. (lpr)

12/13/22 Reviewed by Avalon 3rd Quarter 2022 CAB. Medical Director review 11/2022. Edited "when covered" section for clarity. No change to policy statement. Updated policy guidelines and references. Deleted AHS-M2109 from related policies section. (lpr)