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Corporate Medical Policy

Gene Expression Profiling for Uveal Melanoma AHS - M2071

File Name:	gene_expression_profing_for_uveal_melanoma
Origination:	1/1/2019
Last CAP Review:	6/2019
Next CAP Review:	6/2020
Last Review:	12/2019

Description of Procedure or Service

Uveal melanomas (UM) develop 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 that guide their management (Albert, Ryan, & Borden, 1996; Gragoudas, Lane, Shih, & Carvajal, 2017).

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 (Spira, 2017). Gene expression profiling has been proposed as a method of risk stratification for uveal melanoma.
******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 gene expression profiling for 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 Gene Expression Profiling for Uveal Melanoma is covered

1. Gene expression profiling for uveal melanoma using tests such as DecisionDx-UM is considered medically necessary for patients with primary, localized uveal melanoma.
2. The following genetic markers for uveal melanoma are considered medically necessary for patients with primary, localized uveal melanoma:
    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 Gene Expression Profiling for Uveal Melanoma is not covered

Gene expression profiling for uveal melanoma is considered investigational in all other situations, including all other gene expression profiling tests (eg. DecisionDx-PRAME) or genetic analysis for genetic markers not listed above (eg.DecisionDx-UMSeq).

Policy Guidelines

Uveal melanoma 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), as 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 ("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," 2001; Carvajal et al., 2014; 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 uveal melanoma (J. William Harbour & Chen, 2017).

UM typically presents with visual disturbance, but may be asymptomatic (Mahendraraj et al., 2016). The diagnosis of uveal melanoma 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 uveal melanoma is not completely characterized but is not associated with the frequent BRAF mutations of cutaneous melanoma. Uveal melanoma has been associated with activating mutations in GNAQ or GNA11 in greater than 80 percent of primary uveal melanomas 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 uveal melanoma(J. W. Harbour et al., 2010). Germline mutations of BAP1 in approximately 5 percent of patients with uveal melanomas 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 (Gragoudas et al., 2017; J. W. Harbour et al., 2013; Martin et al., 2013).

Clinical Validity and Utility
Genetic analysis of uveal melanoma 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.

In 2010 Onken et al developed and validated PCR-based 15-gene GEP assay comprising 12 discriminating genes and three endogenous control genes, analyze the technical performance of the assay, and evaluated the prognostic accuracy of the assay (Onken, Worley, Tuscan, & Harbour, 2010).

In 2012 Onken et al “evaluated the prognostic performance of a 15 gene (GEP) assay that assigns primary posterior uveal melanomas to prognostic subgroups” and found 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

(Onken et al., 2012) allowing patients to be stratified into risk categories such that high-risk patients can be offered intensive metastatic surveillance and adjuvant therapy while low-risk patients can be spared these interventions and costs (J. William Harbour & Chen, 2017).

Randomized trials of patients with high risk of uveal melanoma recurrence showed no difference in survival between patients treated with adjuvant therapy versus no adjuvant treatment and regular screening tests for the development of liver metastases have not shown evidence of any effect on patient outcomes (Augsburger, Corrêa, & Shaikh, 2008). However, cytogenetics and gene expression profiling based molecular classification significantly enhanced prognostication of patients with uveal melanoma, allowing detection of patients at high risk for metastases and stratification of patients for entry into clinical trials of emerging adjuvant therapy (Jovanovic et al., 2013).

Regarding staging and prognosis, Gragoudas et al (2017) stated that "the use of chromosomal markers in the tumor (ie, monosomy of chromosome 3) have some utility for predicting prognosis, but these markers, as well as clinical and histopathological markers of prognosis, are less reliable than gene expression profiling to define groups at high-risk for subsequent development of metastatic disease."

Correa and Augsberger (2016) conducted a prospective case series study of 299 patients to evaluate if any conventional clinical prognostic factors for metastasis from uveal melanoma have prognostic value in multivariate models incorporating GEP class of the tumor cells. The researchers found that GEP class was the strongest prognostic factor for metastatic death in this series. Additionally, tumor LBD, tumor thickness, and intraocular tumor location also proved to be significant individual prognostic factors. The authors concluded that "both GEP and LBD of the tumor are independent prognostic factors for metastasis and metastatic death in multivariate analysis."

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 compared to Class 2 patients (5% versus 36%, resp.; median follow-up of 27.3 months) that confirms the clinical utility of DecisionDx-UM.
In a review of the clinical management of uveal and conjunctival melanoma, Blum et al (2016) stated that "although there is no clear survival benefit from earlier detection of metastatic disease, patients could benefit from clinical trial eligibility and palliative therapy with earlier detection"

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."

Onken et al (2012) conducted a prospective, multicenter study with 459 patients to evaluate the prognostic performance of a 15-gene expression profiling assay that assigns primary posterior uveal melanomas to two prognostic subgroups: class 1 (low metastatic risk) and class 2 (high metastatic risk). The GEP assay successfully classified 446 of 459 cases (97.2%). 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." However, the study did not report if the results of the GEP assay was used in clinical management of the study participants.

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 uveal melanoma."
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)(Nathan et al., 2015)(Nathan et al., 2015)(Nathan et al., 2015.

Cai et al (2018) compared the prognostic accuracy of gene expression profiling with PRAME status and TNM staging in patients with Uveal Melanoma. They found that GEP was Class 1 in 128 (53.3%) cases, and Class 2 in 112 (46.7%) cases. PRAME status was negative in 157 (65.4%) cases and positive in 83 (34.6%) cases. TNM was stage I in 26 (10.8%) cases, IIA in 67 (27.9%) cases, IIB in 50 (20.8%) cases, IIIA in 59 (24.6%) cases and IIIB in 38 (15.8%) cases. Metastatic disease was detected in 59 (24.6%) cases after median follow-up of 29 months (mean 42 months; range 1-195 months). Variables associated with metastasis included (in order of decreasing significance): GEP class (P=1.5 x 10-8), largest basal tumor diameter (P=2.5 x 10-6), PRAME status (P=2.6 x 10-6), and TNM stage (P=3.7 x 10-6). The prognostic accuracy of an optimized 3-category GEP/PRAME model (P = 8.6 × 10-14) was superior to an optimized TNM model (P = 1.3 × 10-5).

Kucherlapati (2018) examine small groups of genes with known biology in replication and repair at the transcriptional and genomic levels, correlating alterations with survival in uveal melanoma tumor progression and found that 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 previously identified as a cancer variant, and reportedly used as an early serum biomarker in lung cancer was found. Mismatch Repair protein MLH3 was found to have splicing variations with deletions to both Exon 5 and Exon 7 simultaneously. PCNA, FEN1, and LIG1 had increased relative expression levels not due to mutation or to copy number variation.

Szalai et al (2018) examined the stochastic properties of primary uveal melanoma including the mutation rate as a function of tumor size and metastatic rate relative to the type of mutation. Based on the 5-year metastatic rates, mutation rates ranged from 1.09 × 10-8 to 7.86 × 10-7 per cell division, using our calculation algorithm. A higher mutation rate was found for tumors with smaller thicknesses. EIF1AX mutations were not exclusive of other mutations because 2 cases with EIF1AX mutations and metastasis also had BAP1 mutations. None of the tumors with only an EIF1AX mutation metastasized. After plotting the yearly metastatic rate vs time after treatment, we observed a small peak at 1 year and a large peak at 3.5 years after treatment for BAP1 mutations, with peaks between 2 and 3 years and at 7 years for SF3B1 mutations.

State and Federal Regulations, as applicable
This test is considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories.

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.

National Comprehensive Cancer Network (NCCN)
The NCCN published its first guidelines for Uveal Melanoma in 2018. They recommend risk stratification in follow up and after metastasis by genetic testing, screening for mutations that may be potential targets for treatment or determine eligibility for a clinical trial. Consider broader genomic profiling if the test results might guide future decisions or eligibility for a clinical trial (NCCN, 2018).

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 uveal melanoma characteristics." (AJCC, 2015).

National Institute for Health and Clinical Excellence (NICE) Guidelines
NICE Guidelines (Nathan et al., 2015) state that: "Prognostic factors of uveal melanoma 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 uveal melanoma but there is insufficient comparative data. No evidence was found that demonstrated one technique was superior to another."

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: 0081U, 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

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Specialty Matched Consultant Advisory Panel 6/2019

Medical Director review 11/2019

Policy Implementation/Update Information

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)