BlueCross BlueShield Federal Employee Program.

FEP 2.04.120 Gene Expression Profiling for Uveal Melanoma

Effective Date: July 15, 2018

Related Policies:
8.01.10 Charged-Particle (Proton or Helium Ion) Radiotherapy for Neoplastic Conditions

Gene Expression Profiling for Uveal Melanoma

Description

Uveal melanoma is associated with a high rate of metastatic disease, and survival after the development of metastatic disease is poor. Prognosis following treatment of local disease can be assessed using various factors, including clinical and demographic markers, tumor stage, tumor characteristics, and tumor cytogenetics. Gene expression profiling (GEP) can be used to determine prognosis, and gene expression profile testing is commercially available.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). The DecisionDx-UM® test (Castle Biosciences, Phoenix, AZ) is available under the auspices of the Clinical Laboratory Improvement Amendments. Exome or genome sequencing tests as a clinical service are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

POLICY STATEMENT

Gene expression profiling for uveal melanoma with DecisionDx-UM is **medically necessary** for patients with primary, localized uveal melanoma.

Gene expression profiling for uveal melanoma that do not meet the above criteria is **investigational.**

POLICY GUIDELINES

Genetic Analysis

Genetic analysis of uveal melanoma can provide prognostic information for the risk of developing metastatic disease. Prescher et al (1996) showed that monosomy of chromosome 3 correlated strongly with metastatic death, with a 5-year survival reduction from 100% to 50%.[11] Subsequent studies have reported that, based on genetic analysis, there were 2 distinct types of uveal melanomas—those with monosomy chromosome 3 associated with a very poor prognosis and those with disomy 3 and 6p gain associated with a better prognosis.[1] The *BAP1* gene has been identified as an important marker of disease type. In 1 study (2016), 89% of tumors with monosomy 3 had a *BAP1* variant, and no tumors without monosomy 3 had a *BAP1* variant.[12]

Gene expression profiling determines the expression of multiple genes in a tumor and has been proposed as an additional method to stratify patients into prognostic risk groups.

BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

RATIONALE

Summary of Evidence

For individuals who have localized uveal melanoma who receive a GEP test for uveal melanoma (DecisionDx-UM), the evidence includes cross-sectional studies of assay validation and clinical validity. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, other test performance measures, functional outcomes, health status measures, and quality of life. One commercially available test identified (DecisionDx-UM) has published data related to its clinical validity, and is the focus of this review. Three studies of clinical validity identified used the GEP score to predict melanoma metastases and melanoma-specific survival. All three reported that GEP classification correlated strongly with metastatic disease and melanoma mortality. Two studies compared GEP classification with other prognostic markers, and GEP class had the strongest association among the markers tested. GEP classification appears to be a strong predictor of metastatic disease and melanoma death. There are no studies directly showing clinical utility. Absent direct evidence, a chain of evidence can be constructed to determine whether using the results of GEP testing for management decisions improves the net health outcome of patients with uveal melanoma. Aaberg et al (2014) have shown an association between GEP classification and treatment, reporting that patients classified as low-risk were managed with less frequent and intensive surveillance and were not referred for adjuvant therapy. It is uncertain whether stratification of patients into higher risk categories has the potential to improve outcomes by allowing patients to receive adjuvant therapies through detection of metastases earlier. However, classification into the low-risk group would support a reduction in the burden of surveillance without apparent harm. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

In its guidelines on melanoma (v.1.2018), the National Comprehensive Cancer Network states: "Mucosal and uveal melanomas differ significantly from cutaneous melanoma in presentation, genetic profile, staging, response to treatment, and patterns of progression. Ideally, mucosal and uveal melanoma should be treated as diseases distinct from cutaneous melanoma, with care tailored to the individual."[16]

Melanoma Focus

Melanoma Focus, a British medical nonprofit that focuses on melanoma research, published guidelines on uveal melanoma in 2015.[17] These guidelines, which were created using a process accredited by the

National Institute for Health and Care Excellence, contained the following statements on prognosis and surveillance.

"*3.5.1 Prognostic factors/tools*

1. Prognostic factors of uveal melanoma are multi-factorial and include clinical, morphological and genetic features. The following features should be recorded:
   - Age
   - Gender
   - Tumour location
   - Tumour height
   - Tumour Largest [sic] basal diameter
   - Ciliary body involvement
   - Extraocular melanoma growth (macroscopic)

The following features should be recorded if tissue is available:

- Cell type (modified Callender system)
- Mitotic count (number/40 high power fields in H&E [hematoxylin and eosin] stained sections)
- Presence of extravascular matrix patterns (particularly closed connective tissue loops; enhanced with Periodic acid Schiff staining). Grade A
- Presence of extraocular melanoma growth (size, presence or absence of encapsulation). [GRADE A]

3.5.2 Prognostic biopsy

1. There should be a fully informed discussion with all patients, explaining the role of biopsy including the benefits and risks. The discussion should include:
   - Risk of having the biopsy
   - Limitations of the investigation
   - Benefits for future treatments (including possible recruitment to trials)
   - Impact on quality of life…
   - Follow-up [GPP]…
2. Use of the current (i.e. 7th) Edition of the TN staging system for prognostication is highly recommended. Grade A
3. Use of multifactorial prognostication models incorporating clinical, histological, immunohistochemical and genetic tumour features - should be considered. Grade D

3.6 Surveillance

1. Prognostication and surveillance should be led by a specialist multidisciplinary team that incorporates expertise from ophthalmology, radiology, oncology, cancer nursing and hepatic services. [GPP]
2. Prognostication and risk prediction should be based on the best available evidence, taking into account clinical, morphological and genetic cancer features. [GPP]
3. All patients, irrespective of risk, should have a holistic assessment to discuss the risk, benefits and consequences of entry into a surveillance programme. The discussion should consider risk of false positives, the emotional impact of screening as well as the frequency and duration of screening. An individual plan should be developed. [GPP]
4. Patients judged at high-risk of developing metastases should have 6-monthly life-long surveillance incorporating a clinical review, nurse specialist support and liver specific imaging by a non-ionising modality. [GPP] …
5. Liver function tests alone are an inadequate tool for surveillance. Grade C"

Note that Melanoma Focus defined GPP as a recommended best practice based on the clinical experience of the guideline development group.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

1. Spagnolo F, Caltabiano G, Queirolo P. Uveal melanoma. *Cancer Treat Rev.* Aug 2012;38(5):549-553. PMID 22270078
2. Finger RL. Intraocular melanoma. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. 10th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2014:1770-1779.
3. Hawkins BS. Collaborative ocular melanoma study randomized trial of I-125 brachytherapy. *Clin Trials.* Oct 2011;8(5):661-673. PMID 22013172
4. Pereira PR, Odashiro AN, Lim LA, et al. Current and emerging treatment options for uveal melanoma. *Clin Ophthalmol.* Sep 2013;7:1669-1682. PMID 24003303
5. Francis JH, Patel SP, Gombos DS, et al. Surveillance options for patients with uveal melanoma following definitive management. *Am Soc Clin Oncol Educ Book.* May 2013:382-387. PMID 23714555
6. Diener-West M, Reynolds SM, Agugliaro DJ, et al. Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: Collaborative Ocular Melanoma Study Group Report No. 26. *Arch Ophthalmol.* Dec 2005;123(12):1639-1643. PMID 16344433
7. Correa ZM. Assessing prognosis in uveal melanoma. *Cancer Control.* Apr 2016;23(2):93-98. PMID 27218785
8. Nathan P, Cohen V, Coupland S, et al. Melanoma Focus: Uveal Melanoma National Guidelines: Summary. 2015; http://melanomafocus.com/wp-content/uploads/2015/06/Uveal-Melanoma-National-Guidelines-Summary-v1.3.pdf. Accessed January 9, 2018.
9. Finger PT, AJCC-UICC Ophthalmic Oncology Task Force. The 7th edition AJCC staging system for eye cancer: an international language for ophthalmic oncology. *Arch Pathol Lab Med.* Aug 2009;133(8):1197-1198. PMID 19653708
10. AJCC Ophthalmic Oncology Task Force. International validation of the American Joint Committee on Cancer's 7th Edition Classification of Uveal Melanoma. *JAMA Ophthalmol.* Apr 2015;133(4):376-383. PMID 25555246
11. Prescher G, Bornfeld N, Hirche H, et al. Prognostic implications of monosomy 3 in uveal melanoma. *Lancet.* May 4 1996;347(9010):1222-1225. PMID 8622452
12. van de Nes JA, Nelles J, Kreis S, et al. Comparing the prognostic value of BAP1 mutation pattern, chromosome 3 status, and BAP1 immunohistochemistry in uveal melanoma. *Am J Surg Pathol.* Jun 2016;40(6):796-805. PMID 27015033
13. Choudhary MM, Gupta A, Bena J, et al. Hepatic ultrasonography for surveillance in patients with uveal melanoma. *JAMA Ophthalmol.* Feb 2016;134(2):174-180. PMID 26633182
14. McLean IW, Berd D, Mastrangelo MJ, et al. A randomized study of methanol-extraction residue of bacille Calmette-Guerin as postsurgical adjuvant therapy of uveal melanoma. *Am J Ophthalmol.* Nov 15 1990;110(5):522-526. PMID 2240139
15. Desjardins L, Dorval T, Levy C, et al. Etude randomisée de chimiothérapie adjuvante par le Déticène dans le mélanome choroïdien (Randomized study of adjuvant therapy by DTIC in choroidal melanoma). *Ophtalmologie.* 1998;12(3):168-173. PMID
16. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Melanoma. Version 1.2018. https://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf. Accessed December 19, 2017.
17. Nathan P, Cohen V, Coupland S, et al. Uveal Melanoma UK National Guidelines. *Eur J Cancer.* Nov 2015;51(16):2404-2412. PMID 26278648
18. Onken MD, Worley LA, Tuscan MD, et al. An accurate, clinically feasible multi-gene expression assay for predicting metastasis in uveal melanoma. *J Mol Diagn.* Jul 2010;12(4):461-468. PMID 20413675

19. Onken MD, Worley LA, Ehlers JP, et al. Gene expression profiling in uveal melanoma reveals two molecular classes and predicts metastatic death. *Cancer Res.* Oct 15 2004;64(20):7205-7209. PMID 15492234
20. Onken MD, Worley LA, Char DH, et al. Collaborative Ocular Oncology Group report number 1: prospective validation of a multi-gene prognostic assay in uveal melanoma. *Ophthalmology.* Aug 2012;119(8):1596-1603. PMID 22521086
21. Walter SD, Chao DL, Feuer W, et al. Prognostic implications of tumor diameter in association with gene expression profile for uveal melanoma. *JAMA Ophthalmol.* Jul 01 2016;134(7):734-740. PMID 27123792
22. Decatur CL, Ong E, Garg N, et al. Driver mutations in uveal melanoma: associations with gene expression profile and patient outcomes. *JAMA Ophthalmol.* Jul 01 2016;134(7):728-733. PMID 27123562
23. Plasseraud KM, Cook RW, Tsai T, et al. Clinical performance and management outcomes with the DecisionDx-UM gene expression profile test in a prospective multicenter study. *J Oncol.* 2016;2016:5325762. PMID 27446211
24. Aaberg TM, Jr., Cook RW, Oelschlager K, et al. Current clinical practice: differential management of uveal melanoma in the era of molecular tumor analyses. *Clin Ophthalmol.* Jan 2014;8:2449-2460. PMID 25587217

POLICY HISTORY

Date	Action	Description
September 2014	New Policy	Gene expression profiling for uveal melanoma is considered investigational.
September 2015	Update Policy	Policy updated with literature review through April 28, 2015; no references added. Policy statement unchanged.
December 2016	Update Policy	Policy updated with literature review through April 29, 2016; references 2-4, 6-9, 11, 14, and 16-18 added. Policy statement unchanged.
March 2017	Update Policy	Policy updated with literature review through February 2, 2017; references 5-7, 22, and 24 added. Policy statement changed to medically necessary for patients with localized uveal melanoma
June 2018	Update Policy	Policy updated with literature review through December 11, 2017; no references added. Policy statement unchanged.