DecisionDx Uveal Melanoma

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Introduction

DecisionDX testing for uveal melanoma is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
DecisionDx-PRAME	81401
DecisionDx Uveal Melanoma Gene Expression Profile	81552

Criteria

Introduction

Requests for DecisionDX testing for uveal melanoma are reviewed using the following criteria.

DecisionDX-UM

DecisionDx-UM testing is medically necessary when the following criteria are met:
- No previous DecisionDx-UM testing performed after current diagnosis when a result was successfully obtained, AND
- Member has primary, localized uveal melanoma, AND
- No evidence of metastatic disease, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

DecisionDx-PRAME

This test is considered Experimental, Investigational, or Unproven.

- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.
- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

DecisionDx-UMSeq

For information on DecisionDX-UMSeq testing, please refer to the guideline *Somatic Mutation Testing*, as this testing is not addressed here.

What is Uveal Melanoma?

Uveal melanoma (UM) is a rare cancer of the eye, arising in the choroid, ciliary body or iris of the eye, with about 1500 new cases per year in the US. It accounts for about 5% of all melanomas in the US.[1]

- The diagnosis is usually established by clinical assessment combined with ancillary diagnostic testing, using fluorescein angiography and ultrasonography.[2]
- Despite relatively high cure rates of the primary tumor following treatment,[3] metastatic disease to the liver occurs in 20 to 50% of individuals with UM. Median survival after metastasis detection has been reported to be approximately 9 months.[4]
- As a result, accurate prognostic assessment for metastatic risk is considered crucial for an individual's survival. Conventional prognostic evaluation of UM involves clinical and pathologic criteria, such as age, tumor diameter, tumor thickness, ciliary body involvement, tumor cell morphology, extracellular matrix patterning, and extraocular tumor extension.[4,5]
- Some experts have questioned the accuracy of these methods to predict metastasis.[6,7] As such, new molecular techniques examining the genetic composition of tumor cells have been introduced to improve prognostic evaluations potentially allowing for more targeted surveillance and treatment options for UM. Additionally, it may also facilitate referral of high-risk individuals to clinical trials.[7,8]

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Test information

Introduction

DecisionDx-UM is a 15 gene panel that measures gene expression of 12 genes present in ocular melanoma (CDH1, ECM1, EIF1B, FXR1, HTR2B, ID2, LMCD1, LTA4H, MTUS1, RAB31, ROBO1, and SATB1) and 3 control genes (MRPS21, RBM23, and SAP130). This test is designed to assess the risk of metastasis within 5 years.[9]

- DecisionDx-UM test results are reported as follows:[9,10]

  ◦ Class 1A – very low risk (2%) of metastasis within 5 years
  ◦ Class 1B – intermediate risk (21%) of metastasis within 5 years
  ◦ Class 2 – high risk (72%) of metastasis within 5 years

- DecisionDx-PRAME is a test that can be added on to the DecisionDx-UM assay for additional information regarding prognosis. According to Castle Biosciences,"PRAME [preferentially expressed antigen in melanoma] is usually not expressed in normal adult tissues, but in some cancers, PRAME expression is elevated. Studies have suggested that elevated PRAME expression ("PRAME positive") in a Class 1 uveal melanoma tumor may be associated with an increased risk of metastasis compared to a Class 1 tumor that does not express PRAME ("PRAME negative")."[11]
- The manufacturer also offers the DecisionDX-UMSeq test.[12,13]

Guidelines and evidence

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2024) stated the following regarding gene expression for uveal melanoma.[8]

- "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. Biopsy is typically performed before the tumor is irradiated and can often be performed at the time of primary treatment depending on the procedure modality. If biopsy is performed, molecular/chromosomal testing for prognostication is preferred over cytology alone. The risk/benefits of biopsy for prognostic analysis should be carefully considered and discussed."
- "For patients who had a biopsy of their primary tumor, certain molecular features have been shown to be prognostic for risk of distant spread and should be used for risk stratification."
- Gene expression profiling as described by Onken et al[14] was recommended as part of the stratification in determining the class of the tumor [Class 1A (low risk), Class 1B (medium risk), or Class 2 (high risk)] to inform frequency of follow-up.

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- ◦ "It has been shown that class 2 was associated with a 5-fold to 20-fold higher risk of metastasis than class 1."
- "PRAME expression, present in about a third of uveal melanomas has also been associated with increased risk of metastasis. … PRAME expression is also an indicator of high risk to be used to inform frequency of follow-up."

Selected Relevant Publications

Based on the review of the available peer-reviewed published literature, the DecisionDx-UM 15-gene assay has sufficient evidence for use as a prognostic test in individuals diagnosed with primary, localized uveal melanoma to assist clinicians with predicting disease severity and improving disease management strategies.[3,14-28]

DecisionDX-PRAME

There is currently insufficient evidence regarding use of DecisionDX-PRAME.[29-34] Clinical validity and clinical utility studies are lacking. Additional studies are needed to determine whether DecisionDX-PRAME improves clinical outcomes more than DecisionDX-UM alone. As a result, no conclusions can be drawn regarding the value and usefulness of this test.

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for DecisionDX Uveal Melanoma will ensure that testing will be available to those members most likely to benefit from the information provided by the assay. For those not meeting criteria, it ensures alternate management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

References

1. Chattopadhyay C, Kim DW, Gombos DS, et al. Uveal melanoma: From diagnosis to treatment and the science in between. *Cancer*. 2016;122(15):2299-2312.
2. National Cancer Institute (NCI). Intraocular (Eye) Melanoma Treatment. Available at: **https://www.cancer.gov/types/eye/hp/intraocular-melanoma-treatment-pdq**
3. 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. doi:10.1155/2016/5325762.
4. Harbour JW. A prognostic test to predict the risk of metastasis in uveal melanoma based on a 15-gene expression profile. *Methods Mol Biol.* 2014;1102:427-440. doi: 10.1007/978-1-62703-727-3_22.
5. Walter SD, Chao DL, Feuer W, et al. Prognostic implications of tumor diameter in association with gene expression profile for uveal melanoma. *JAMA Ophthalmol.* 2016;134(7):734-740. doi: 10.1001/jamaophthalmol.2016.0913.

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6. Chappell MC, Char DH, Cole TB, et al. Uveal melanoma: molecular pattern, clinical features, and radiation response. *Am J Ophthalmol.* 2012;154(2):227-232.e222. doi: 10.1016/j.ajo.2012.02.022.

7. Schopper VJ, Correa ZM. Clinical application of genetic testing for posterior uveal melanoma. *Int J Retina Vitreous.* 2016;2:4. doi: 10.1186/s40942-016-0030-2.

8. Swetter SM, Johnson D, Albertini M, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2024 - May 23, 2024. Melanoma: Uveal, available at: **https://www.nccn.org/professionals/ physician_gls/pdf/uveal.pdf** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Melanoma: Uveal V1.2024 - May 23, 2024. ©2024 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines®, go online to NCCN.org.

9. Castle Biosciences, Inc. Understanding the results. Available at:

    https://castlebiosciences.com/patient-information/ophthalmology/uveal-melanoma/test-process-and-results

10. Castle Biosciences, Inc. Overview of DecisionDx-UM. Available at:

    https://castlebiosciences.com/tests/prognostic/decisiondx-um/how-it-works

11. Castle Biosciences, Inc. DecisionDx-PRAME Summary. Available at:

    https://castlebiosciences.com/tests/prognostic/decisiondx-um/prame

12. Castle Biosciences, Inc. DecisionDx-UMSeq Summary. Available at:

    https://castlebiosciences.com/tests/prognostic/decisiondx-um/umseq

13. Castle Biosciences, Inc. Test Requisition Form. Available at:

    https://castlebiosciences.com/Sample%20Report%20and%20Order%20Form/DDxMelanoma-Reqform-FINAL-FILLABLE-0623.pdf

14. Onken MD, Worley LA, Char DH, et al. Collaborative ocular oncology group report No. 1: prospective validation of a multi-gene prognostic assay in uveal melanoma. *Ophthalmology.* 2012;119(8):1596-1603.

15. Aaberg TM, Jr., Cook RW, Oelschlager K, Maetzold D, Rao PK, Mason JO III. Current clinical practice: differential management of uveal melanoma in the era of molecular tumor analyses. *Clin Ophthalmol.* 2014; 8: 2449-2460.

16. Augsburger JJ, Correa ZM, Augsburger BD. Frequency and implications of discordant Gene Expression Profile class when posterior uveal melanomas are sampled by Fine Needle Aspiration Biopsy at two sites. *Am J of Ophthalmol.* 2015;159(2):248-256.

17. Berger AC, Davidson RS, Poitras J, et al. Clinical impact of a 31-gene expression profile test for cutaneous melanoma in 156 prospectively and consecutively tested patients. *Curr Med Res Opin.* 2016; 32(9):1599-1604.

18. Correa ZM, Augsburger JJ. Sufficiency of FNAB aspirates of posterior uveal melanoma for cytologic versus GEP classification in 159 patients, and relative prognostic significance of these classifications. *Graefe's Arch Clin Exp Ophthalmol.* 2014; 252:131-135.

19. Harbour JW, Chen R. The DecisionDx-UM Gene Expression Profile Test provides risk stratification and individualized patient care in uveal melanoma. *PLOS Curr.* 2013 Apr 9.

20. Onken MD, Worley LA, Tuscan MD, Harbour JW. An accurate, clinically feasible multi-gene expression assay for predicting metastasis in uveal melanoma. *JMD.* 2010;12(4):461-468.

21. Klufas MA, Richter E, Itty S, et al. Comparison of gene expression profiling and chromosome 3 analysis by fluorescent in situ hybridization and multiplex ligation probe amplification in fine-needle aspiration biopsy specimens of uveal melanoma. *Ocul Oncol Pathol.* 2017;4(1):16-20.

22. Miller AK, Benage MJ, Wilson DJ, Skalet AH. Uveal melanoma with histopathologic intratumoral heterogeneity associated with gene expression profile discordance. *Ocul Oncol Pathol.* 2017;3(2):156-160.

23. Valsecchi ME, Orloff M, Sato R, et al. Adjuvant sunitinib in high-risk patients with uveal melanoma: comparison with institutional controls. *Ophthalmology.* 2018;125(2):210-217.

24. Aaberg TM, Covington KR, Tsai T, et al. Gene expression profiling in uveal melanoma: five-year prospective outcomes and meta-analysis. *Ocul Oncol Pathol.* 2020;6(5):360-367. doi:10.1159/000508382.

25. Schefler AC, Skalet A, Oliver SC, et al. Prospective evaluation of risk-appropriate management of uveal melanoma patients informed by gene expression profiling. *Melanoma Manag.* 2020;7(1):MMT37. doi:10.2217/ mmt-2020-0001.

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26. Augsburger JJ, Skinner CC, Correa ZM. Comparative metastatic rates in GEP Class 1A versus 1B Posterior Uveal Melanoma: Results contrary to expectations. *Ocul Oncol Pathol*. 2023;8(4-6):242-249. doi: 10.1159/000526770

27. Miguez S, Lee RY, Chan AX, et al. Validation of the prognostic usefulness of the gene expression profiling test in patients with uveal melanoma. *Ophthalmology.* 2023;130(6):598-607. doi: 10.1016/j.ophtha.2023.01.020

28. Suwajanakorn D, Lane AM, et al. Impact of gene expression profiling on diagnosis and survival after metastasis in patients with uveal melanoma. *Melanoma Res*. 2024 Aug 1;34(4):319-325. doi: 10.1097/CMR.0000000000000971

29. Field MG, Durante MA, Decatur CL, et al. Epigenetic reprogramming and aberrant expression of PRAME are associated with increased metastatic risk in Class 1 and Class 2 uveal melanomas. *Oncotarget*. 2016;7(37):59209-59219.

30. Field MG DC, Decatur CL, Kurtenbach S, et al. PRAME as an independent biomarker for metastasis in uveal melanoma. *Clin Cancer Res*. 2016;22(5):1234-1242.

31. Schefler AC, Koca E, Bernicker EH, Correa ZM. Relationship between clinical features, GEP class, and PRAME expression in uveal melanoma. *Graefes Arch Clin Exp Ophthalmol*. 2019;257(7):1541-1545.

32. Cai L, Paez-Escamilla M, Walter SD, et al. Gene expression profiling and PRAME status versus Tumor-Node-Metastasis staging for prognostication in uveal melanoma. *Am J Ophthalmol*. 2018;195:154-160. doi: 10.1016/j.ajo.2018.07.045

33. Alsoudi AF, Skrehot HC, Chévez-Barrios P, et al. Comprehensive molecular profiling of uveal melanoma evaluated with gene expression profiling, preferentially expressed antigen in melanoma expression, and next-generation sequencing. *Retina*. 2024;44(9):1580-1589. doi: 10.1097/iae.0000000000004153

34. Harbour JW, Correa ZM, Schefler AC, et al. 15-Gene expression profile and PRAME as integrated prognostic test for uveal melanoma: first report of Collaborative Ocular Oncology Group Study No. 2 (COOG2.1). *J Clin Oncol*. 2024;42(28):3319-3329. doi: 10.1200/jco.24.00447

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