# FEP Medical Policy Manual

## FEP 2.04.120 Gene Expression Profiling for Uveal Melanoma

### Annual Effective Policy Date: July 1, 2024

### Original Policy Date: September 2014

### Related Policies:

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

## Gene Expression Profiling for Uveal Melanoma

### Description

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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.

## OBJECTIVE

The objective of this evidence review is to assess whether net health outcomes are improved when gene expression profile testing is used to determine the prognosis of individuals with uveal melanoma compared to determining prognosis without gene expression profile testing.

## POLICY STATEMENT

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

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

## POLICY GUIDELINES

None

## BENEFIT APPLICATION

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

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.

## FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests 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 CLIA. Laboratories that offer laboratory-developed tests must be licensed by the 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.

## RATIONALE

### Summary of Evidence

For individuals who have localized uveal melanoma who receive a gene expression profiling (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. Six studies of clinical validity identified used the GEP score to predict melanoma metastases and melanoma-specific survival. All 6 reported that GEP classification correlated strongly with metastatic disease and/or melanoma mortality. Four 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 of 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 an improvement in the net health outcome.

## SUPPLEMENTAL INFORMATION

## Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

# National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines (v1.2023 ) for uveal melanoma state that if biopsy is performed, "molecular/chromosomal testing for prognostication is preferred over cytology alone." The guidelines include DecisionDx-UM classes as 1 of the factors used to risk-stratify patients for systemic imaging and note that risk stratification to determine the frequency of follow-up should be based on the highest risk factor present.[12,]

# Melanoma Focus

In 2015, Melanoma Focus, a British medical nonprofit that focuses on melanoma research, published guidelines on uveal melanoma.[13,] These guidelines, which were created using a process accredited by NICE, contained the following statements on prognosis and surveillance. A 2022 guideline update included several additional relevant statements, which are denoted with (2022).[27,]The guidance for surveillance was updated in 2023; relevant statements are denoted with (2023).

"4.2 Genetic and molecular features (2022)

*Prognostic factors/tool*

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).

- Presence of extraocular melanoma growth (size, presence or absence of encapsulation).

- Positive or negative expression of nuclear BAP1 protein in the tumour cells. (2022)

2. The following features should be recorded if cytology of tumour is available:

- Confirmation of melanoma cells (i.e., exclude differential diagnoses, particularly metastatic carcinoma) - immunocytology may be required for this, but is not always necessary.

- Cell type (modified Callender system), if possible. (2022)

*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:

- Enabling prognostication and allow tailored follow-up

- Allowing recruitment into adjuvant trials

- Risks of having the biopsy

- Limitations of the investigation

- Effects of prognostication information on quality of life (2022)

2. The minimum dataset for uveal melanoma from the Royal College of Pathology (or national official equivalents) should be recorded in the pathology reports. [...]

3. Use the most up-to-date edition of the Tumor Node Metastasis staging system for prognostication and include in pathology/clinical reports. (2022)

4. Collect molecular genetic and/or cytogenetic data for research and prognostication purposes, where tumour material is available and where patient consent has been obtained, as part of an ethically-approved research programme. (2022)

5. The use of multifactorial prognostication models incorporating clinical, histological, immunohistochemical and genetic tumour features should be considered. (2022)

6. Where available the results of state-of-the-art molecular analysis should be combined with clinical features and standard anatomical and pathological staging for prognostication. (2022)

7. Tests for novel circulating blood-borne biomarkers should only be used within clinical trials or research programmes. (2022)

[...]

4.4 Surveillance

*Ocular surveillance for tumour recurrence and any other ocular morbidity*

1. Patients should be offered surveillance of the eye initially every 6 months for 2 to 5 years and then annually depending on response to therapy and individual patient factors. If there is doubt over stability, then the interval between follow-ups can be reduced to allow for a period of closer follow up to either confirm or refute stability. (2023)

*Liver Surveillance*

1. Patients should be offered a discussion with an oncologist or other appropriately trained healthcare professional to discuss the relative merits of metastatic surveillance. For patients who commence surveillance this should be co-ordinated through secondary care and not primary care. (2023)

2. A multi-parameter prognostic model (e.g. LUMPO) should be used in discussion with uveal melanoma patients with respect to their individual metastatic risk, and value of liver surveillance during follow up. (2023)

3. For patients without genetic analyses, modelling with LUMPO to estimate risk with or without monosomy 3 may inform discussion around risk of recurrence and value of imaging surveillance. (2023)

4. Patients who are considered to have a less than 10% metastatic risk within a 10-year period as calculated by a multi-parameter prognostic model (e.g. LUMPO) should not be recommended for regular liver surveillance. (2023)

5. The decision to start surveillance and the duration should be individualised based on factors such as co-morbidity and fitness to act on the results of scan findings. (2023)

6. Standard surveillance should be for 10 years from the initial ocular diagnosis. This should be every 6 months for 5 years and then annually to 10 years. The choice of imaging modality should be discussed with the patient but should be focused on the liver. (2023)

7. When available, patients with a known somatic SF3B1 mutation (not routinely tested at the time of this guidance) may benefit from extending surveillance for 15 years. (2023)

8. Liver function tests are an inadequate tool for surveillance for uveal melanoma metastases and should not be part of routine surveillance. (2023)

## U.S. Preventive Services Task Force Recommendations

Not applicable.

# Medicare National Coverage

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

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## POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

| Date | Action | Description |
|---|---|---|
| September 2014 | New policy | Gene expression profiling for uveal melanoma is considered investigational |
| September 2015 | Replace policy | Policy updated with literature review through April 28, 2015; no references added. Policy statement unchanged. |
| December 2016 | Replace 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 | Replace 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 | Replace policy | Policy updated with literature review through December 11, 2017; no references added. Policy statement unchanged. |
| June 2019 | Replace policy | Policy updated with literature review through December 4, 2018. Reference to new NCCN guidelines specific to uveal melanoma added. Policy statement unchanged. |
| June 2020 | Replace policy | Policy updated with literature review through December 9, 2019; reference on NCCN guidelines updated. Policy statement unchanged. |
| June 2021 | Replace policy | Policy updated with literature review through November 17, 2020; references added. Policy statements unchanged. |
| June 2022 | Replace policy | Policy updated with literature review through January 7, 2022; no references added. Policy statements unchanged. |
| June 2023 | Replace policy | Policy updated with literature review through December 16, 2022; references added. Minor editorial refinements to policy statements; intent unchanged. |
| June 2024 | Replace policy | Policy updated with literature review through December 19, 2023; no references added. Policy statements unchanged. |