Gene Expression Profiling for Uveal Melanoma

Summary
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. This evidence review addresses whether outcomes are improved when GEP testing is used to determine prognosis of patients with uveal melanoma compared to determining prognosis without GEP testing.

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 is 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 is considered investigational.

BENEFIT APPLICATION
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 gene expression profiling (GEP) test for uveal melanoma, 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. There is limited published data on the analytic validity of GEP testing. Three studies of clinical validity identified used the GEP score to predict melanoma metastases and melanoma-specific survival. All 3 reported that GEP
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class correlated strongly with metastatic disease and melanoma mortality. Two studies compared GEP class to other prognostic markers, and GEP class had the strongest association among the markers tested. GEP class appears to be a strong predictor of metastatic disease and melanoma death, but it is uncertain whether its use for management decisions will improve the net health outcome. Aaberg et al (2014) showed 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. Although classification into the low-risk group may reduce the burden of surveillance, it has not been shown for patients who are considered to be at high risk for metastases that adjuvant treatment or more intensive surveillance improves survival or morbidity outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Commercially Available Testing
The DecisionDx-UM test (Castle Biosciences, Phoenix, AZ) is a GEP test intended to assess 5-year metastatic risk in uveal melanoma. The test was introduced in late 2009, and claims to identify the molecular signature of a tumor and its likelihood of metastasis within 5 years. The assay determines the expression of 15 genes, which stratify a patient’s individual risk of metastasis into 2 classes. Based on the clinical outcomes from the prospective, 5-year multicenter Collaborative Ocular Oncology Group study, the DecisionDx-UM test reports class 1A, class 1B, and class 2 phenotypes:
- Class 1A: Very low risk, with a 2% chance of the eye cancer spreading over the next 5 years;
- Class 1B: Low risk, with a 21% chance of metastasis over 5 years;
- Class 2: High risk, with 72% odds of metastasis within 5 years.

Practice Guidelines and Position Statements

U.K. national guidelines for uveal melanoma were published in 2015. These guidelines contain the following statements related to prognosis and surveillance.

**Prognostic factors/tools**

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]

**Prognostic biopsy**

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
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- Limitations of the investigation
- Benefits for future treatments (including possible recruitment to trials)
- Impact on quality of life
- Recruitment to trials
- Follow-up [GPP]

The minimum dataset for uveal melanoma from the Royal College of Pathology should be recorded. http://www.rcpath.org/publicationsmedia/publications/datasets/uveal-melanoma.htm Grade D

Tests for novel serological biomarkers should only be used within clinical trials or research programs. [GPP]

Consider collecting molecular genetic and/or cytogenetic data for research and prognostication purposes where tumor material is available and where patient consent has been obtained as part of an ethically approved research program. [GPP]

Use of the current (i.e. 7th) Edition of the TNM staging system for prognostication is highly recommended. Grade A

Use of multifactorial prognostication models incorporating clinical, histological, immunohistochemical and genetic tumour features - should be considered. Grade D

Surveillance

Prognostication and surveillance should be led by a specialist multidisciplinary team that incorporates expertise from ophthalmology, radiology, oncology, cancer nursing and hepatic services. [GPP]

Prognostication and risk prediction should be based on the best available evidence, taking into account clinical, morphological and genetic cancer features. [GPP]

All patients, irrespective of risk, should have a holistic assessment to discuss the risk, benefits and consequences of entry into a surveillance program. 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]

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]

Liver function tests alone are an inadequate tool for surveillance. Grade C

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

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### POLICY HISTORY

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<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tr>
<td>September 2014</td>
<td>New Policy</td>
<td>Policy updated with literature review; no references added.</td>
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<tr>
<td>September 2015</td>
<td>Update Policy</td>
<td>Policy statement unchanged.</td>
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<tr>
<td>December 2016</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 29, 2016; references 2-4, 6-9, 11, 14, and 16-18 added. Policy statement unchanged.</td>
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*Signature on File*

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