Gene Expression Profiling for Uveal Melanoma

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Replaces 2.04.120

Policy

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 does not meet the above criteria is investigational.

Related Policies

None

Policy Guidelines

Examples of commercial tests include:

- DecisionDx-UM® test (Castle Biosciences Inc., Phoenix, AZ)

Coding

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
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<tbody>
<tr>
<td>81599</td>
<td>unlisted multianalyte assays with algorithmic analyses</td>
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</table>

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.
Background

**Uveal melanoma**
The uveal tract is the middle layer of the wall of the eye, and has 3 main parts: the choroid (a tissue layer filled with blood vessels), ciliary body (muscle tissue that changes the shape of the pupil and the lens), and the iris (the colored part of the eye). Uveal melanoma arises from melanocytes in the stroma of the uveal tract. Approximately 90% of uveal melanomas arise in the choroid, 7% in the ciliary body, and 3% in the iris.(1)

Uveal melanoma, although rare, is the most common primary intraocular malignancy in adults. Mean age-adjusted incidence of uveal melanoma in the United States is 6.3 per million people among whites, 0.9 among Hispanics, and 0.24 among blacks.(1) Uveal melanoma has a progressively rising, age-specific, incidence rate that peaks near age 70. Host susceptibility factors associated with the development of this cancer include white race, fair skin, and light eye color.

**Treatment**
Treatment of primary, localized uveal melanoma can be by surgery or radiotherapy. In general, larger tumors require enucleation surgery and smaller tumors can be treated with radiotherapy, but specific treatment parameters are lacking. The most common treatment of localized uveal melanoma is radiotherapy, which is preferred because it can spare vision in most cases. For smaller lesions, randomized controlled trials (RCTs) have shown that patients receiving radiotherapy or enucleation progress to metastatic disease at similar rates after treatment.(2,3) Radiotherapy can be delivered by various mechanisms, most commonly brachytherapy and proton beam therapy.(1,2) Treatment of primary uveal melanoma improves local control and spares vision, however, the 5-year survival rate (81.6%) has not changed over the last 3 decades, suggesting that life expectancy is independent of successful local eye treatment.(4)

Uveal melanomas disseminate hematogenously, and metastasize primarily to the liver and lungs. Treatment of hepatic metastases is associated with prolonged survival and palliation in some patients. Therapies directed at locoregional treatment of hepatic metastases include surgical and ablative techniques, embolization, and local chemotherapy.

**Surveillance for Metastatic Disease**
It is unusual for patients with uveal melanoma to have distant metastases at presentation, with less than 1% presenting with metastases when they are treated for their intraocular disease, but they are at risk for distant metastases, particularly to the liver, for years after presentation.(5) The prospective, longitudinal Collaborative Ocular Melanoma Study (COMS) study followed 2320 patients with choroidal melanoma with no melanoma metastasis at baseline who were enrolled in RCTs to evaluate forms of radiotherapy for choroidal melanoma for 5 to 10 years.(6) During follow-up, 739 patients were diagnosed with at least 1 site of metastasis, of which 660 (89%) were liver. Kaplan-Meier estimates of 2-, 5-, and 10-year metastasis rates were 10% (95% confidence interval [CI], 9% to 12%), 25% (95% CI, 23% to 27%), and 34% (95% CI, 32% to 37%), respectively.

The optimal method and interval for surveillance are not well-defined, and it has not been established in prospective trials whether surveillance identifies metastatic disease earlier. Potential methods for metastases include magnetic resonance imaging, ultrasound, liver function testing, and positron emission tomography scans. One 2016 retrospective study of 262 patients estimated that use of hepatic ultrasound and liver function testing every 6 months in individuals with treated local uveal melanoma would yield a sensitivity and specificity for a diagnosis of metastasis of 83% (95% CI, 44% to 97%) and 100% (95% CI, 99% to 100%), respectively.(7)

Identifying patients at high risk for metastatic disease might assist in selecting patients for adjuvant treatment and more intensive surveillance for metastatic disease, if such changes lead to improved outcomes. Adjuvant treatment for metastatic disease consists of radiotherapy or systemic therapy, such as chemotherapy, immunotherapy, hormone therapy, biological therapy, or targeted therapy. Randomized trials of patients with high risk for uveal melanoma recurrence have shown no differences in survival rates between patients treated with and without adjuvant therapy. However, these trials were reported in 1998 and 1990,(8,9) and may not be representative of current treatment and risk-stratification methods.
Prognosis
Metastatic disease is the leading cause of death in patients with uveal melanoma, and approximately 50% of patients will develop distant metastasis. A number of factors may be used to determine prognosis, but the optimal approach is uncertain.\textsuperscript{(10,11)} The most important clinical factors that predict metastatic disease are tumor size measured in diameter or in thickness, ciliary body involvement, and transscleral extension. Clinical staging according to the American Joint Committee on Cancer (AJCC) recommendations allows risk stratification for metastatic disease.\textsuperscript{(12)} In a retrospective study of 3377 patients with uveal melanoma, in which staging was performed using AJCC classifications, the rate of metastases-free survival at 5 years was 97% for stage I, 89% for stage IIA, 79% for stage IIB, 67% for stage IIIA, 50% for stage IIIB, and 25% for stage IIIB.\textsuperscript{(13)}

Genetic Analysis
Genetic analysis of uveal melanoma can provide prognostic information for the risk of developing metastatic disease. In 1996, Prescher et al showed that monosomy of chromosome 3 correlated strongly with metastatic death, with a 5-year survival reduction from 100% to 50%.\textsuperscript{(14)} Subsequent studies reported the initial idea 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.\textsuperscript{(1)} The \textit{BAP1} gene has been identified as an important marker of disease type. In 1 study, 89% of tumors with monosomy 3 had a \textit{BAP1} mutation, and no tumors without monosomy 3 had a \textit{BAP1} mutation.\textsuperscript{(15)} Gene 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.

Commercially Available Testing
DecisionDx-UM is a GEP test intended to assess 5-year metastatic risk in uveal melanoma. The test was introduced in 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 3 classes. The 15-gene signature was originally developed based on a hybridization-based microarray platform; the current commercially available version of the DecisionDx-UM test is a polymerase chain reaction–based test that can be performed on fine-needle aspirate samples.

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.

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\textregistered 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.

Scope

Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
This policy was created in May 2014, with the most recent literature review of the MEDLINE database through February 2, 2017. This policy addresses BCBSA genetic testing category 2c on prognostic testing of cancer cells from an affected individual to benefit the individual. The primary question addressed by this review is whether the use of gene expression profiling (GEP) to determine prognosis following initial treatment of uveal melanoma improves outcomes compared to determining prognosis by alternative approaches.

Uveal Melanoma

Clinical Context and Test Purpose
The purpose of using the DecisionDx-UM test in individuals with localized uveal melanoma is to inform a decision about how often patients should undergo follow-up for metastases, based on their likelihood of developing metastases.

Analytic Validity
Augsburger et al (2015) reported on the correlation between GEP classifications when samples from 2 sites from the same tumor were tested.(16) This prospective, single-center study enrolled 80 patients who had uveal melanoma resection. Tumor samples were taken from 2 different sites and GEP testing was performed independently on both samples. The primary measure reported was the rate of discordance between the 2 samples on GEP class. Nine (11.3%) cases (95% confidence interval [CI], 9.0% to 13.6%) were definitely discordant and 13 (16.3%) cases were definitely or possibly discordant (95% CI, 13.0% to 19.6%). Thus the heterogeneity of tumor and limitations to sampling may explain cases of misclassification where GEP results do not accurately predict prognosis.

In 2010, Onken et al validated the GEP assay from a microarray platform to a polymerase chain reaction–based 15-gene assay comprised of 12 discriminating genes and 3 endogenous control genes from previously published data sets.(17,18) Technical performance of the assay was analyzed in a prospective study of 609 previously untreated tumors. Tumor samples were obtained by fine-needle aspiration (n=553) or after enucleation (n=56). Samples were used for cytologic examination and RNA analysis. The genes were tested on the authors’ training set of 28 uveal melanomas (15 considered to be of prognostic class 1 and 13 in class 2), with clinical follow-up of at least 5 years. The gene assay was demonstrated to be of sufficient sensitivity, failing on 1 of 51 samples with a cytologic diagnosis of quantity not sufficient, and preliminary outcome data affirmed the prognostic accuracy of the assay. The authors concluded, based on preliminary outcome data available for samples collected from 172 patients with a median follow-up of 16 months, that the assay identified which patients would develop metastatic disease (p=1.9×10^-6).

Section Summary
There is little published data on the analytic validity of GEP testing. One study has reported validation data of tumor samples from 172 patients using preliminary outcomes data over a median of 16 months as well as results from a training set of 28 samples with at least 5-year follow-up. A second study examined the discordance in GEP classification when 2 samples of the same tumor were tested, and reported discordance in 11.3% to 16.3% of cases. However, this design is more informative of sampling issues in the face of tumor heterogeneity and does not address the main question of analytic validity: Does repeated testing of the same sample yields confirmatory or discordant results?
Clinical Validity

Three studies reported data on the association of GEP score with clinical outcomes; they are summarized in Table 1. All studies showed strong and positive associations between GEP class and clinical outcomes.

The first study was published in 2012 by Onken et al. This prospective, multicenter study evaluated the prognostic performance of a 15-gene GEP assay in patients with posterior (choroidal and ciliary body) uveal melanoma. (19) Prognostic groups were class 1 (low risk of metastasis) or class 2 (high risk of metastasis). 459 cases were enrolled from 12 centers between June 2006 and November 2010. The GEP assay rendered a classification in 97.2% of cases. GEP testing results were class 1 in 276 (61.9%) cases and class 2 in 170 (38.1%) cases. Mean follow-up was 18.0 months (median, 17.4 months). Metastasis was detected in 3 (1.1%) of class 1 cases and 44 (25.9%) of class 2 cases (p <0.001). By univariate Cox proportional hazard analysis, factors associated with metastatic disease included advanced patient age (p=0.02), ciliary body involvement (p=0.03), tumor diameter (p<0.001), tumor thickness (p=0.006), chromosome 3 status (p<0.001), and GEP class (p<0.001). The GEP test was associated with a significant net reclassification index (NRI) over TNM classification for survival at 2 years (NRI=0.37, p=0.008) and 3 years (NRI=0.43, p=0.001).

Two other studies reporting data on clinical validity were published in 2016. (20,21) Walter et al evaluated 2 cohorts of patients at 2 clinical centers who underwent resection for uveal melanoma. (20) This study had similar methodology to Onken (2012). (19) The primary cohort included 339 patients, of which 132 patients were also included in the Onken (2012) study, along with a validation cohort of 241 patients, of which 132 were also included in the Onken study, the latter group of which was used to test a prediction model using the GEP plus pretreatment largest basal diameter. Cox proportional hazards analysis was used in the primary cohort to examine GEP classification and other clinicopathologic factors (tumor diameter, tumor thickness, age, sex, ciliary body involvement, pathologic class). GEP class 2 was the strongest predictor of metastases and mortality. Tumor diameter was also an independent predictor of outcomes, using a diameter of 12 mm as the cutoff value. In the validation cohort, GEP results were class 1 (61.4%) in 148 patients and class 2 (38.6%) in 93 patients. Again, GEP results were most strongly associated with progression-free survival.

Decatur et al (2016) was a smaller, retrospective study of 81 patients who had tumor samples available from resections occurring between 1998 and 2014. (21) GEP was class 1 in 35 (43%) patients, class 2 in 42 (52%) patients, and unknown in 4 (5%) patients. GEP class 2 was strongly associated with BAP1 variants (r=0.70; p<0.001). On Cox proportional hazards analysis, GEP class 2 was the strongest predictor of metastases and melanoma mortality (see Table 1).

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Rate of Metastases</th>
<th>Melanoma Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>GEP Class 1</td>
<td>GEP Class 2</td>
</tr>
<tr>
<td>Onken (2012)</td>
<td>459 pts with UM from 12 clinical centers</td>
<td>1.1%</td>
<td>25.9%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Walter (2016)</td>
<td>Primary cohort: 339 pts from 2 clinical centers with UM arising in ciliary body or choroid</td>
<td>5.8%</td>
<td>39.6%</td>
</tr>
<tr>
<td></td>
<td>Validation cohort: 241 patients from 2 clinical centers with UM arising in ciliary body or choroid</td>
<td>2.7%</td>
<td>31.2%</td>
</tr>
<tr>
<td>Decatur (2016)</td>
<td>81 pts from a single center with available tumor samples of UM arising from ciliary body or choroid</td>
<td>2.7%</td>
<td>31.2%</td>
</tr>
</tbody>
</table>

GEP: gene expression profile; NR: not reported; pts: patients; UM: uveal melanoma.

<sup>a</sup> p<0.001.

<sup>b</sup> Reported as relative risk (95% confidence interval) for metastases (or melanoma mortality) in group 2 vs group 1.

Section Summary

There are 3 published studies on clinical validity included in this review. These studies have reported that GEP class 2 is a strong predictor of metastases and melanoma survival, and also strongly correlates with PAB1 mutations. Two studies have compared GEP class to clinicopathologic features and have reported that GEP class is the strongest predictor of clinical outcomes.
Clinical Utility
Direct evidence of clinical utility is provided by studies that compare health outcomes for patients managed with and without the test. Preferred evidence comes from randomized controlled trials.

There is no direct evidence that use of DecisionDx-UM for the selection of patients for different surveillance outcomes improves health outcomes. Absent direct evidence, a chain of evidence can be developed based on the clinical validity of the test.

The GEP test is associated with risk of metastatic disease and melanoma death. Although the 3 available studies reporting on clinical validity do not all specifically report on rates of survival or metastasis risk by risk group, there is clearly an association of risk category and metastasis and death. For a rare cancer, the studies on clinical validity include a large proportion of annual incident cases.

Plasseraud et al (2016) reported metastasis surveillance practices and patient outcomes using data from a prospective observational registry study of DecisionDx-UM conducted at 4 centers, which included 70 patients at the time of reporting. Surveillance regimens were documented by participating physicians as part of registry data entry. “High-intensity” surveillance was considered to be imaging and/or liver function testing (LFTs) every 3 to 6 months and “low-intensity” surveillance was considered to be annual imaging and/or LFTs. The method for following patients for clinical outcomes was not specified. Of the 70 enrolled patients, 37 (53%) were class 1. Over a median follow up of 2.38 years, more class 2 patients (36%) than class 1 patients (5%; p=0.002) experienced a metastasis. The 3-year metastasis-free survival (MFS) rate was lower for class 2 patients (63%; 95% CI, 43% to 83%) than class 1 patients (100%; CI not specified; p=0.003). Most class 1 patients (n=30) had low-intensity surveillance and all (n=33) class 2 patients had high-intensity surveillance. Strengths of this study included a relatively large population given the rarity of the condition, and an association between management strategies and clinical outcomes. However, it is not clear which outcome measures were prespecified or how data was collected, making the risk of bias high.

Aaberg et al (2014) reported on changes in management associated with GEP risk classification. They analyzed Medicare claims data submitted to Castle BioSciences by 37 ocular oncologists in the United States. Data were abstracted from charts on demographics, tumor pathology and diagnosis, and clinical surveillance patterns. High-intensity surveillance was defined as a frequency of every 3 to 6 months and low-intensity surveillance was a frequency of every 6 to 12 months. Of 195 patients with GEP test results, 88 (45.1%) patients had evaluable tests and adequate information on follow-up surveillance, 36 (18.5%) had evaluable tests and adequate information on referrals, and 8 (4.1%) had evaluable tests and adequate information on adjunctive treatment recommendations. Of the 191 evaluable GEP tests, 110 (58%) were class 1 and 81 (42%) were class 2. For patients with surveillance data available (n=88), all patients in GEP class 1 had low-intensity surveillance and all patients in GEP class 2 had high-intensity surveillance (p<0.001 vs class 1).

It is likely that treating liver metastasis has an effect on local symptoms and survival, for at least a subset of patients. However, it is uncertain whether the surveillance interval has an effect on the time to detection of metastases.

There is the potential for patients considered to be at high risk for metastases to undergo adjuvant treatment, but to date no adjuvant therapies for non-metastasized uveal melanomas have been shown to reduce the risk of metastasis.

Section Summary
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. GEP classification appears to be a strong predictor metastatic disease and melanoma death. 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 or through the detection of metastases earlier. However, classification into the low-risk group would permit reduction in the burden of surveillance without apparent harm.
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. 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 classification correlated strongly with metastatic disease and melanoma mortality. Two studies compared GEP classification to other prognostic markers, and GEP class had the strongest association among the markers tested. GEP classification appears 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 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.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tbody>
<tr>
<td>Ongoing</td>
<td></td>
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<tr>
<td>NCT02376920</td>
<td>5 Year Registry Study to Track Clinical Application of DecisionDx-UM Assay Results and Associated Patient Outcomes (CLEAR)</td>
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<td>Oct 2020</td>
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</tbody>
</table>

NCT: national clinical trial.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network
In its guidelines on melanoma (v.1.2017), the National Comprehensive Cancer Network (NCCN) 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.”(24)

Melanoma Focus
Melanoma Focus, a British medical nonprofit that focuses on melanoma research, published guidelines on uveal melanoma in 2015.(25) 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
2. 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
   - Recruitment to trials
   - Follow-up [GPP]
2. The minimum dataset for uveal melanoma from the Royal College of Pathology should be recorded. https://www.rcpath.org/asset/44EB109E-3E3D-4704-B7B57F86F657BA09/ Grade D
3. Tests for novel serological biomarkers should only be used within clinical trials or research programmes. [GPP]
4. Consider collecting 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. [GPP]
5. Use of the current (ie, 7th) Edition of the TNM staging system for prognostication is highly recommended. Grade A
6. 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: 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
References


Appendix

N/A

History

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<td>08/11/14</td>
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<td>07/14/15</td>
<td>Annual Review. Policy updated with literature review through April 28, 2015; no references added. Policy statement unchanged.</td>
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<td>10/01/16</td>
<td>Annual Review, approved September 13, 2016. 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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<td>05/01/17</td>
<td>Annual review, approved April 11, 2017. Policy updated with literature review through February 2, 2017; references 5-7, 22, and 24 added. Policy statement changed from investigational to medically necessary for patients with primary, localized uveal melanoma.</td>
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U.S. Department of Health and Human Services
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본 통지서에는 중요한 정보가 있습니다. 이 통지서는 특별히 밀집된 정보가 포함되어 있습니다. 통지서의 일부분은 특정 기간에 이행할 필요가 있습니다. 귀하의 언어를 사용한 정보를 제공하기 위해 800-722-1471 (TTY: 800-842-5357)로 전화해 주십시오.

Русский (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas claras en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

日本語 (Japanese):
この通知には重要な情報が含まれています。この通知には、Premera Blue Crossの申請または補償範囲に関する重要な情報が含まれている場合があります。この通知には記載されている情報が有効な日付をご確認ください。健康保険料や有料サービスを維持するには、特定の期日にまでに行動を取らなければなりません。お問い合わせの際には、この情報をお手伝いすることを念頭においてください。（800-722-1471 (TTY: 800-842-5357)）

Română (Romanian):

Українська (Ukrainian):
Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страхувального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на вашій рідній мові. Дозвоніться за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):