IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Gene expression assays have been created to aid risk stratification in patients with melanoma.

MEDICAL POLICY CRITERIA

I. The DecisionDx-UM™ gene expression assay may be considered medically necessary in patients with primary, localized uveal melanoma.

II. The DecisionDx-UM™ gene expression assay is considered investigational for patients that do not meet criterion I.

III. All other gene expression assays for melanoma are considered investigational, including but not limited to DecisionDX-Melanoma™, Pigmented Lesion Assay, and myPath Melanoma™.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.
• Name of the genetic test(s) or panel test
• Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
• The exact gene(s) and/or mutations being tested
• Relevant billing codes
• Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
• Medical records related to this genetic test
  o History and physical exam
  o Conventional testing and outcomes
  o Conservative treatment provided, if any

CROSS REFERENCES
1. Genetic Testing for Cutaneous Malignant Melanoma, Genetic Testing, Policy No. 08
2. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
3. Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer, Genetic Testing, Policy No. 42

BACKGROUND

CUTANEOUS MELANOMA

Cutaneous melanoma represents less than 5% of skin malignancies but results in the most skin cancer deaths. The incidence of cutaneous melanoma continues to increase, and it is currently the sixth most common cancer in the United States. Standard treatment options for stage I and II melanoma are excision with or without sentinel lymph node examination. Current risk factors to predict localized tumor aggression include Breslow tumor thickness, tumor ulceration, and mitotic rate of the tumor cells. Regional lymph node involvement, the likelihood of which increases with increasing tumor thickness, significantly negatively impacts the rate of survival.

UVEAL MELANOMA

Uveal melanoma (UM), also referred to as ocular or choroidal melanoma, is the most common, but rare, primary ocular malignancy in adults and shows a strong tendency for metastases to the liver. Approximately four million cases of UM occur each year.[1] Even with successful treatment of the primary tumor, up to 50% of individuals subsequently develop systemic metastases, with liver involvement in up to 90% of these individuals. Despite aggressive systemic treatments, metastatic liver disease remains the most common cause of tumor-related mortality in choroidal malignant melanoma, with a median survival time of two to seven months and a one-year survival rate of less than 10%. The primary clinical issue in the management of UM is accurately predicting risk of metastasis.

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. 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.

COMMERCIALLY AVAILABLE TESTING
The DecisionDx-Melanoma™ is a gene expression profile test that is a signature of 31 genes, 28 discriminating genes, and 3 control genes. The test is used to measure risk of metastasis in patients with stage I and II cutaneous melanoma and classifies tumors into two groups of risk of metastasis, high or low (class 1 and 2, respectively). The test purports to give an independent prediction of risk of tumor metastatic risk, independent of currently used metrics of risk assessment (e.g., Breslow’s thickness, ulceration status, and mitotic rate; American Joint Committee on Cancer stage, sentinel lymph node biopsy status), so that patients with high-risk stage I or II disease can possibly undergo more aggressive surveillance treatment than they would have otherwise received.

The DecisionDx-UM™ test (Castle Biosciences Inc.) is a commercially marketed gene expression profiling test intended for use in assessing metastatic risk in individuals with this condition. It consists of a 15-gene polymerase chain reaction (PCR)-based assay that stratifies individuals with UM into two classes based on the molecular signature of tumor tissue. Uveal melanomas cluster into two molecular groups based on their gene expression profile. Tumors with the class 1 signature rarely metastasize, whereas those with the class 2 signature metastasize at a high rate. Class 1 tumors have been further distinguished into class 1a (lowest metastatic risk) and class 1b (moderate long-term metastatic risk).

According to Castle Biosciences Inc., the DecisionDx-UM™ test results are used for the following:

- To initiate referral to a medical oncologist for treatment planning which may include adjuvant treatment.
- To develop specific monitoring or surveillance plans:
  - More frequent monitoring with advanced imaging procedures may be recommended for those individuals identified as having a high risk of developing metastasis.
  - For individuals at a low risk of developing metastasis, a less intensive surveillance plan may balance the risks of radiation exposure associated with less frequent imaging.
- To improve life-planning.

REGULATORY STATUS

The DecisionDx tests are performed in a Clinical Laboratory Improvement Amendment (CLIA)-certified laboratory and do not require U.S. Food and Drug Administration (FDA) clearance.

Note: Microarray-based gene expression analysis of prostate cancer and breast cancer are addressed in separate medical policies (see Cross References).

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[^2] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:
1. Analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;  
2. Clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and  
3. Clinical utility, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Review of the literature focused on identifying evidence related to clinical validity and clinical utility, particularly whether the tests can be used to improve treatment planning compared with the standard of care, and whether their use results in improved health outcomes.

CUTANEOUS MELANOMA

Clinical Validity

To develop the DecisionDx-Melanoma gene panel, Gerami conducted a meta-analysis of published studies that identified differential gene expression in metastatic versus nonmetastatic primary cutaneous melanoma. Of 54 identified genes, investigators selected 20 for further PCR analysis based on chromosomal location. Five genes from the DecisionDx-Uveal Melanoma gene panel were added based on analysis of metastatic and nonmetastatic primary cutaneous melanoma, and 2 probes (for both the 3’ and 5’ ends) of the BRCA1-associated protein one gene, BAP1, which has been associated with the metastatic potential of uveal melanoma, also were added. Finally, four genes with minimal variation in expression level between metastatic and nonmetastatic primary cutaneous melanoma were added as controls. The 31-gene panel was applied to three cohorts using archived formalin-fixed, paraffin-embedded primary cutaneous melanoma tissue. Patients had minimum follow-up of five years unless there was a well-documented metastatic event, including positive sentinel lymph node biopsy. Information about treatments received was not provided.

The first cohort (development set) included 107 patients with stage 1 or 2 primary melanoma from three U.S. centers. The second and third cohorts included 161 additional patients with stage 0-4 disease from seven U.S. centers (total N=268). Thirty-four patients (20%) without evidence of metastasis had less than five years of follow-up. For 78 patients in the third cohort (test set) with AJCC stage 1 or 2 cutaneous melanoma who had either a metastatic event or more than 5 years of follow-up without metastasis, 5-year DFS was 98% for class 1 patients and 37% for class 2 patients; PPV and NPV were 67% and 94%, respectively. For 220 patients with AJCC stage 1 or 2 cutaneous melanoma in the combined training and test cohorts, DecisionDx-Melanoma classified 84% of patients who did not develop metastasis as class 1 and 89% of patients who developed metastasis as class 2 (sensitivity, 90%; specificity, 84%; PPV=72%; NPV=95%). Median duration of follow-up for these 220 patients was not reported.

In 2015, Gerami reported the outcomes of a multicenter cohort study comparing the prognostic accuracy of gene expression profiling (GEP) and sentinel lymph node biopsy (SLNB) in 217 patients with cutaneous melanoma (CM). GEP was reported to be a better predictor than SLNB (p<.0001) and, when combined with SLNB, improved prognostication. However, these results were preliminary and require verification in additional studies. In addition, the impact of these results on health outcomes needs to be studied. A major limitation of this study was that the overall risk of metastatic events was about 30% higher in the SLNB-negative cohort of patients than is usually found in the general CM population.
Clinical Utility

Berger (2016) published a retrospective study of 156 consecutive patients from six institutions who had cutaneous melanoma and were evaluated with the DecisionDx-Melanoma test.[5] This study used chart review to describe changes in management, and examined whether management changes were associated with DecisionDx-Melanoma results. The frequency of clinic visits, imaging tests, referrals, and blood work was measured before and after results of DecisionDx were available. For patients with class 1 results there was reduced utilization in 40/42 patients, and for patients with class 2 results there was increased utilization for 74/79. The difference in management changes by test class was statistically significant (p<0.0001).

UVEAL MELANOMA

Clinical Validity

Augsburger (2015) reported on the correlation between GEP classifications when samples from two sites from the same tumor were tested.[6] This prospective, single-center study enrolled 80 patients who had uveal melanoma resection. Tumor samples were taken from two different sites and GEP testing was performed independently on both samples. The primary measure reported was the rate of discordance between the two samples on GEP class. Nine (11.3%) cases were definitely discordant (95% confidence interval [CI], 9.0% to 13.6%), 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 revalidated the GEP assay when it was migrated from a microarray platform to a polymerase chain reaction–based 15-gene assay comprised of 12 discriminating genes and three endogenous control genes from previously published data sets collected from the same group.[7,8] Technical performance of the assay was assessed in 609 tumor samples, including 553 fine needle aspiration biopsies and 56 enucleation specimens from the authors' laboratory (n=188) and 11 collaborating sites (n=421). According to the study protocol, sample failure rate due to incorrect specimen handling was low, occurring in 32 of 609 (5.3%) of samples (p<0.0001). Preliminary data suggested the potential for increased sensitivity of gene expression profiling compared with cytologic diagnosis, as the assay failed in only one of 51 (2%) of samples with insufficient material for cytological diagnosis; however, point estimates of overall test accuracy (e.g., sensitivity, specificity, or both) were not provided. In a subset of 172 individuals with UM, the relationship between tumor class and metastasis was studied with available clinical data and a median follow-up time of 16 months. Within this group, the assay was reported to correctly identify individuals who went on to develop metastatic disease. Kaplan-Meier analysis showed approximately 24% class 2 individuals with UM surviving at 48 months and close to 100% survival in the class 1 group, although more specific data was not provided. This study evaluated primarily fine needle aspiration biopsy specimens (553 of 609, or 90.8%) rather than enucleation specimens; however, the data reported on the relationship between tumor class and metastasis are limited, and median follow-up time was reported as a relatively short duration (16 months).

In a 2012 prospective, multicenter study by Onken, the prognostic performance of the 15-gene GEP assay was evaluated in 459 patients with posterior UM from 12 independent centers.[9] Tumors were classified by GEP as class 1 or class 2. The first 260 samples were also analyzed for chromosome 3 status using a single nucleotide polymorphism assay. Net reclassification improvement analysis was performed to compare the prognostic accuracy of
GEP with the 7th edition clinical Tumor-Node-Metastasis (TNM) classification and chromosome 3 status. Patients were managed for their primary tumor and monitored for metastasis. The GEP assay successfully classified 446 of 459 cases (97.2%). Metastasis was detected in three class 1 cases (1.1%) and 44 class 2 cases (25.9%) (log-rank test, P<10⁻¹⁴). At 3 years follow-up, the net reclassification improvement of GEP over TNM classification was 0.43 (P = 0.001) and 0.38 (P = 0.004) over chromosome 3 status. The GEP provided a highly significant improvement in prognostic accuracy over clinical TNM classification and chromosome 3 status. The impact of the test results on health outcomes were not identified in the study.

Walter (2016) evaluated two cohorts of patients at two clinical centers who underwent resection for uveal melanoma.[10] This study had similar methodology to 2012 Onken study described above. 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.

Decatur (2016) published a smaller, retrospective study of 81 patients who had tumor samples available from resections occurring between 1998 and 2014.[11] GEP was class 1 in 35 (43%) patients, class 2 in 42 (52%) patients, and unknown in four (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.

Corrêa (2016) performed a single-institution prospective intervention case series to compare the prognostic value of the 15-gene GEP test with other conventional prognostic factors for metastasis and metastatic death, including 299 patients with posterior uveal melanoma evaluated by fine-needle aspiration biopsy at the time of or shortly prior to initial treatment.[12] The cohort in this study had a substantial proportion of patients with smaller tumors compared to previous studies, and this was reflected in the higher proportion of class 1 to class 2 cases in this cohort; 211 (70.6%) class 1 patients and 88 (29.4%) class 2 patients. Step-wise multivariant analysis determined that although GEP class was the strongest prognostic factor for metastatic death in this series; that tumor large basal diameter (LBD) was also a significant prognostic indicator of metastatic death. Kaplan-Meier survival curves demonstrated lower survival in GEP class 2 patients compared with class 1 patients, but survival and metastasis rates by class were not reported.

In 2016, Field did a follow-up study of the 2010 Onken validation cohort, looking at additional biomarkers to complement the DecisionDx-UM GEP test results in 389 consecutive patients.[13] This study analyzed 64 tumor samples previously determined as class 1 in an effort to find independent markers of metastasis in these samples. The investigators reported that class 2 GEP was associated with significantly greater metastatic risk than Class 1 GEP, with metastatic disease being detected in 12/216 (6%) Class 1 cases versus 63/173 (36%) Class 2 cases (p < 0.0001).

### Table 1. Studies of Clinical Validity
### Study Patient Populations

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Populations</th>
<th>Rates of Metastases</th>
<th>Melanoma Mortality Rates</th>
</tr>
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<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%</td>
</tr>
<tr>
<td>Walter (2016)</td>
<td>Primary cohort: 339 pts from one clinical center with UM arising in ciliary body or choroid</td>
<td>5.8%</td>
<td>39.6%</td>
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<td></td>
<td>Validation cohort: 241 pts from one (different) clinical center with UM arising in ciliary body or choroid</td>
<td>2.7%</td>
<td>31.2%</td>
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<tr>
<td>Decatur (2016)</td>
<td>81 pts from a single center with available tumor samples of UM arising in ciliary body or choroid</td>
<td></td>
<td>9.4 (3.1 to 28.5)</td>
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<tr>
<td>Field (2016)</td>
<td>389 pts from two clinical centers with UM arising in ciliary body or choroid</td>
<td>6%</td>
<td>36%</td>
</tr>
</tbody>
</table>

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

### Clinical Utility

To date, there are no published studies that address the specificity, sensitivity, or positive- and negative-predictive values, and no studies that compare patient health outcomes as a result of patient management with versus without this testing. However, a chain of evidence based on the clinical validity of the test can be developed.

Plasseraud (2016) reported metastasis surveillance practices and patient outcomes using data from a prospective observational registry study of DecisionDx-UM conducted at four 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 defined as imaging and/or liver function testing (LFTs) every three to six months and “low-intensity” surveillance was defined as 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%; 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 (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 three to six 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).

**PRACTICE GUIDELINE SUMMARY**

There are no evidence-based clinical practice guidelines which specifically recommend the use of gene expression assays, specifically the DecisionDx assays, to guide the clinical management of patients with malignant tumors.

**NATIONAL COMPREHENSIVE CANCER NETWORK**

The current guidelines from the National Comprehensive Cancer Network (NCCN) for melanoma (version 2.2018[15]) make the following statement: "While there is interest in newer prognostic molecular techniques such as gene expression profiling to differentiate melanomas at low- versus high-risk for metastasis, routine (baseline) prognostic genetic testing of primary cutaneous melanomas (before or following SLNB) is not recommended outside of a clinical study (trial)." These guidelines do not specifically address uveal melanoma.

**AMERICAN BRACHYTHERAPY SOCIETY (ABS)**

The 2014 ABS consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma state the following: “Select centers routinely biopsy uveal melanomas for pathologic, genetic, and molecular biologic analyses. However, patients must be counseled that studies of the ocular and metastatic risks of biopsy have been small, limited in follow-up, single center, and thus did not reach Level 2 Consensus (Uniform panel consensus, based on clinical experience).”[16]

**SUMMARY**

There is enough research to show that the DecisionDX-UM™ genetic test can identify certain patients with uveal melanoma that are at higher risk for their cancer to spread. This information can be used to help determine how often patients should be checked for metastatic disease. Therefore, the DecisionDX-UM™ genetic test may be considered medically necessary for patients with primary, localized uveal melanoma.

There is not enough research to show that the DecisionDX-UM™ genetic test can be useful to measure risk in people with other types of disease, including people with uveal cancer that has spread from another site in the body. Therefore, the DecisionDX-UM™ genetic test is considered investigational in people who do not meet the policy criteria.

There is not enough research to show that any other gene expression tests can help to guide patient management and improve health outcomes for people with melanoma. Therefore, gene expression assays other than the DecisionDX-UM™ test, including but not limited to DecisionDX-Melanoma™, Pigmented Lesion Assay, and myPath Melanoma™, are considered investigational in patients with melanoma.

**REFERENCES**

molecular tumor analyses. *Clinical ophthalmology (Auckland, NZ)*. 2014;8:2449-60. PMID: 25587217


### CODES

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*Date of Origin: April 2013*