HEALTH PLANS
UNIVERSITY OF UTAH

Medical Policy

Genetic Testing for Melanoma

Policy MP-057

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Disclaimer:

1. Policies are subject to change in accordance with State and Federal notice requirements.
2. Policies outline coverage determinations for U of U Health Plans Commercial, and Healthy U (Medicaid) plans. Refer to the "Policy" section for more information.

Description:

Melanoma is a cancer that begins in skin cells called melanocytes. Melanocytes make the brown pigmentation called melanin and are located in the epidermis (top layer of skin). Melanin gives skin a tan or brown color and protects deeper layers of skin from harmful sun rays. Melanoma is more dangerous than other skin cancers as it is much more likely to spread to other parts of the body if not caught and treated early.

Cutaneous melanoma accounts for more than 90% of cases of melanoma. In 2020, more than 100,000 new cases of melanoma are expected to be diagnosed, and more than 6,000 people are expected to die of melanoma.

Uveal melanoma (UM) also may occur though it is a much more uncommon cancer. It is the most common primary intraocular malignancy in adults. Despite excellent local disease control rates with surgery or radiotherapy, up to 50% of UM patients will develop metastatic disease. Following metastasis, the median overall survival is approximately 13 months, with only 8% surviving 2 years. Thus, understanding a patient's metastatic risk is critical so that a risk-appropriate surveillance and management plan can be implemented.

Unlike other skin cancers melanoma has an increased propensity of recurrence and metastases. Thus, the staging of melanoma is important to predict risk of recurrence and guide surveillance and treatment. Current guidelines for staging include evaluating multiple features: tumor thickness, ulceration, regional lymph node status, and metastasis. Staging parameters provide some information of value in disease management, but there is wide variability in rates of metastasis, even for cancers of the same stage, limiting their predictive power.

DecisionDx-Melanoma is a genetic test developed to assist in assessing the risk for recurrence or metastasis of cutaneous based on the presence of specific gene expression. It uses quantitative reverse-transcription PCR (qRT-PCR) to measure the expression of 31 gene regions

to predict risk of metastasis and guide treatment decisions in patients with stage I or II primary cutaneous melanoma.

The DecisionDx-UM test is for patients diagnosed with primary UM, without evidence of metastatic disease, and uses a 15-gene expression profile to identify the likelihood of metastasis within 5 years in patients with UM.

Policy Statement and Criteria

1. Commercial Plans

U of U Health Plans does NOT cover genetic testing for the management of cutaneous malignant melanoma including but not limited to DecisionDx-Melanoma, as it is considered investigational.

U of U Health Plans does NOT cover genetic testing for the management of uveal malignant melanoma or associated with susceptibility, including but not limited to DecisionDx-UM, as it is considered investigational.

2. Medicaid Plans

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

3. Medicare Plans

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicare policies and coverage, please visit their search website at: http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

Clinical Rationale

Cutaneous Melanoma

In 2019, Swetter et al published the updated American Academy of Dermatology (AAD) guidelines for the care and management of primary cutaneous melanoma. Referral for genetic counseling and possible germline genetic testing for select patients with cutaneous melanoma was recommended for consideration with a level IIIC grade of evidence. Although, surgery remains the cornerstone of cutaneous melanoma treatment. The Work Group explained that "there is no strong evidence that genetic evaluation is either harmful or helpful."

The National Comprehensive Cancer Network (NCCN) guidelines on Cutaneous Melanoma (Version 3.2020) states: “Gene expression profiling (GEP) tests are marketed as being able to classify cutaneous melanoma into separate categories based on risk of metastasis. However, it remains unclear whether these tests provide clinically actionable prognostic information when used in addition to or in comparison with known clinicopathologic factors or multivariable nomograms. Furthermore, the impact of these tests on treatment outcomes or follow-up schedules has not been established. Various (mostly retrospective) studies of prognostic GEP testing suggest its role as an independent predictor of worse outcome, though not superior to Breslow thickness or SLN status. The panel does not recommend BRAF or NGS testing for resected stage I–II cutaneous melanoma unless it will inform clinical trial participation. BRAF mutation testing is recommended for patients with stage III at high risk for recurrence for whom future BRAF-directed therapy may be an option. For initial presentation with stage IV disease or clinical recurrence, obtain tissue to ascertain alterations in BRAF, and in the appropriate clinical setting, KIT from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy.” In conclusion, to further define the clinical utility of molecular testing prior to widespread implementation of GEP for prognostication of cutaneous melanoma, and in particular to determine its role in guiding surveillance imaging, SLNB, and adjuvant treatment decisions, additional prospective validation studies are needed.

Also in 2016, a retrospective analysis (Berger et al.) looked at the clinical management changes of 156 patients with cutaneous melanoma, between May 2013 and December 2015, based on the outcome of the 31-gene expression DecisionDx-Melanoma test. Forty-two percent of patients were Stage I, 47% were Stage II and 8% were Stage III. Overall, 95 patients (61%) were Class 1 and 61 (39%) were Class 2. Documented changes in management were observed in 82 (53%) patients, with the majority of Class 2 patients (77%) undergoing management changes compared to 37% of Class 1 patients ($p < 0.0001$ by Fisher's exact test). The majority (77/82, 94%) of these changes were concordant with the risk indicated by the test result ($p < 0.0001$ by Fisher's exact test), with increased management intensity for Class 2 patients and reduced management intensity for Class 1 patients. In conclusion, the study was found limited for the assessment of the impact of gene expression profile based management changes on healthcare resource utilization and patient outcome, as follow-up data was not collected for this patient cohort.

A 2017 study (Ardakani et al) evaluated the ability of comparative genomic hybridization (CGH) to differentiate between melanocytic naevi and melanoma in cases where the two show overlapping histological features. Melanomas are characterized by CNVs, while naevi are normal. The team used 19 formalin fixed, paraffin embedded (FFPE) unambiguous naevi and 19 melanomas, and tested them using a SurePrint G3 Human CGH 8x60K array. CGH was able to differentiate between the naevi and the melanoma in 95% of cases. One nevus showed two large CNV. In conclusion, CGH may be a good adjunctive test to resolve histologically equivocal melanocytic samples, still further studies are needed to demonstrate efficacy.

In 2017, Ferris et al. examined the clinical utility of DermTech’s noninvasive adhesive skin patch test PLA (pigmented lesion assay), which measures 2 gene expressions *LINC00518 and PRAME* for cutaneous melanoma. The study compared the findings of 45 dermatologists who evaluated clinical and dermoscopic images of the lesions tested by PLA and based on their observations, recommended biopsy or not. All samples were biopsied, and readers were blinded to the histopathology. Sixty samples were included that were obtained from March 2014 to November 2015, and determined 8 were melanomas and 52 were non-melanomas. The biopsy concordance using only the dermatologist review was 95%. When the PLA results were included, the biopsy concordance improved to 98.6%. Limitations of the test include not working on the palms of hands, soles of feet, mucous membranes, or nails. In conclusion,

even though the data obtained in this study supports the clinical utility of the PLA test, clinical care will likely be primarily influenced by the nature and location of the pigmented lesion and the need to obtain lesion information beyond clinical or dermatopathology-based image and pattern recognition. Therefore, further studies are needed to obtain relevant data and long-term future objectives beyond the scope of this study.

Then in 2018 Ferris et al. researched further clinical utility, this time in a real world analysis with an observational cohort of 381 patients. The PLA test was positive in 51 patients, and all had a biopsy that resulted in 37% diagnosed with melanoma. In the 330 negative PLA group, nearly all were managed by monitoring. Three had biopsies, and none were found to be melanoma. The authors concluded, 93% of PLA results positive for both LINC00518 and PRAME were diagnosed histopathologically as melanoma. PRAME-only and LINC00518-only lesions were melanomas histopathologically in 50 and 7%, respectively. However, the likelihood of positive histopathologic diagnosis of melanoma appears to be higher in PLA results that are positive for both genes.

A 2018 multi-center trial (Zager et al) organized archived primary melanoma tumors from 523 patients, using a 31 gene expression classifier to classify patients as Class 1 (low risk) and Class 2 (high risk). The 5-year recurrence free survival (RFS) rates for Class 1 and Class 2 were 88% and 52%, respectively. Distant metastasis-free survival rates (DMFS) were 93% for Class 1 versus 60% for Class 2. The gene expression classifier was a significant predictor of RFS and DMFS in univariate analysis in addition to with Breslow thickness, ulceration, mitotic rate, and sentinel lymph node (SLN) status. GEP, tumor thickness and SLN status were significant predictors of RFS and DMFS in a multivariate model that also included ulceration and mitotic rate. In conclusion, even though the GEP test provided value to prognostication, more prospective studies are needed to look at its role for adjuvant therapy in patients.

A 2019 UpToDate review discusses DecisionDX-Melanoma, the commercial gene expression profile test that has been developed for patients with local (stage I and II) or loco-regional (stage III) cutaneous melanoma. However, there is no definitive data regarding its use for risk classification in patients with cutaneous melanoma, nor does this test currently have a role in determining which patients are candidates for adjuvant immunotherapy either as a standard of care or as part of clinical trials.

Hayes Inc., also performed a Molecular Test Assessment on DecisionDx-Melanoma in 2020. Studies which qualified for inclusion in this review included 1 analytical validity study, 5 clinical validity studies and 2 clinical utility studies – 8 studies in all. The analytical validity study of the DecisionDx-Melanoma test demonstrated the assay's reproducibility and technical reliability producing consistent results. However, the review concluded that additional studies are needed for test accuracy measurements. The 5 clinical validity studies provided preliminary evidence that the DecisionDx-Melanoma test predicts metastasis in individuals with stage I or II primary cutaneous melanoma, mainly by comparing survival endpoints between patients designated as class 1 and class 2 by the test. However, most studies included patients not in the intended test population as defined by the laboratory and did not compare gene expression profile results with collective staging features as used in clinical practice. The 2 clinical utility studies observed an impact on management decisions of treating physicians ordering the test. However, the authors found that it is not clear whether DecisionDx-Melanoma adds enough prognostic information to current clinicopathological staging factors to change patient management decisions and ultimately improve outcomes. Also of note is that some or all authors in all studies had financial and/or other relationships with the testing laboratory and all studies were funded by the testing laboratory. In conclusion, the overall quality of the evidence is very low and the studies did not evaluate whether the test provided accurate, clinical actionable information resulting in improved patient outcomes. More

robust studies are needed, that are not sponsored by the lab, to demonstrate a benefit in patient outcomes with the DecisionDx-Melanoma test.

A Systematic Review and Meta-analysis by Marchetti et al of the Current Performance of Gene Expression Profile Tests for Prognosis in Patients with Localized Cutaneous Melanoma was published in JAMA Dermatology in 2020. The authors conclude that "Gene Expression Profile Tests including DecisionDX should still be considered investigational and not reliable as a standard of care in management of melanoma." They summarize that "The prognostic ability of GEP tests among patients with localized melanoma varied by AJCC stage and appeared to be poor at correctly identifying recurrence in patients with stage I disease, suggesting limited potential for clinical utility in these patients".

Furthermore, a consensus statement by Grossman et al published in JAMA Dermatology in 2020 concluded that "More evidence is needed to support using GEP testing to inform recommendations regarding SLNB, intensity of follow-up or imaging surveillance, and postoperative adjuvant therapy. The MPWG (Melanoma Prevention Working Group) recommends further research to assess the validity and clinical applicability of existing and emerging GEP tests".

Uveal Melanoma

Hayes completed a Molecular Test Assessment in June 2020. Only 3 studies met inclusion criteria for review. As it relates to analytic validity, the results of 1 study suggest that there is an established assay process that has been optimized and is reproducible for the DecisionDx-UM test. The assay reproducibility was supported by satisfactory concordance in the class calls. One study was identified that assessed the analytical performance of the current DecisionDx-UM assay that includes 3 risk classes. Plasseraud et al. (2017) assessed the analytical performance of the DecisionDx-UM assay, mainly assay reproducibility comparing the concordance in risk class call (class 1A, 1B, and 2), using fresh frozen fine-needle aspiration biopsy samples and formalin-fixed paraffin-embedded tissue samples. The limitations of the overall evidence to support analytical validity include that other parameters, such as sensitivity (limit of detection), linearity (range of assay concentration that fits within a linear scale), or amplification efficiency (accuracy of amplification) were not reported in the peer-reviewed literature. The impact of intratumor heterogeneity was also not addressed. The biggest strength of the evidence is the laboratory reporting an approximate 5-year technical success rate of 96%. Taken together, there is a very low quality body of evidence supporting the analytical validity of the DecisionDx-UM test.

Related to clinical utility, one study was identified that assessed the clinical utility of the DecisionDx-UM test (Plasseraud et al., 2016). This study reported results from an interim analysis of the ongoing, prospective, multicenter Clinical Application of DecisionDx-UM Gene Expression Assay Results (CLEAR) registry. Although an association between clinical management decisions and DecisionDx-UM risk classes were reported, the role of DecisionDx-UM in physician decisions was not clear. The article included many limitations, and the CLEAR trial study start date was in 2010; thus, it was not clear whether the DecisionDx-UM results used by the physicians included the 2- or 3-risk classification (ClinicalTrials.gov, 2018).

Overall, the quality of the evidence, was judged to be of very low quality to identify the likelihood of metastasis within 5 years in patients with UM. Only 3 studies were identified that provided data for the DecisionDx-UM test that included the 3 risk classes. Although an established assay process is in place, the validity of the test and the impact on patient management is unclear; additional data are needed to support the use of this test.

Applicable Coding

CPT Codes

0089U	Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch (es)
0090U	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a categorical result (i.e., benign, indeterminate, malignant)
81404	Molecular Pathology Procedure Level 5
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (e.g., ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis
84999	Unlisted chemistry procedure

HCPCS Codes

No applicable codes

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