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, CHIP and Healthy U (Medicaid) plans. Refer to the "Policy" section for more information.
3. Services requiring prior-authorization may not be covered, if prior-authorization is not obtained.
4. This Medical Policy does not guarantee coverage or payment of the service. The service must be a benefit in the member's plan and the member must be eligible for coverage at the time of service. Additional payment guidelines may be applied that are not included in this policy.

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 2022, there will be approximately 100,000 new cases of melanoma and more than 7,000 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/CHIP

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 covers genetic testing for the management of primary, localized uveal melanoma, using DecisionDx-UM, as it has been demonstrated to have clinical utility in making treatment decisions.

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: https://medicaid.utah.gov/utah-medicaid-official-publications/ or the Utah Medicaid code Look-Up tool

CPT/HCPCS codes covered by Utah State Medicaid may still require further evaluation to determine medical necessity for coverage.

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. 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. 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.

NCCN Clinical Practice Guidelines related to uveal melanoma notes molecular/chromosomal testing for prognostication is preferred over cytology alone. This is supported in recently published studies but Luo et al., from 2020, DecisionDx-UM is a prognostic test that determines the metastatic risk associated with uveal melanoma (UM). Specifically, the assay determines the activity or “expression” of 15 genes which indicate a patient's individual risk, or class. The test classifies tumors as Class 1 (low metastatic risk) and Class 2 (high metastatic risk). According to the report of the Collaborative Eye Oncology Group (COOG), the DecisionDx-UM GEP test is an accurate prospectively validated molecular classifier whose results are highly correlated with metastatic potential. In a prospective multicenter study, Plasseraud et al demonstrated that the DecisionDx-UM could accurately predict the risk of metastasis in patients with UM.

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

81479 Unlisted molecular pathology procedure

81529 Oncology (cutaneous melanoma), mRNA, gene expression profiling by real-time RT-PCR of 31 genes (28 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk, including likelihood of sentinel lymph node metastasis **(DecisionDx-Melanoma)**

81599 Unlisted multianalyte assay with algorithmic analysis

84999 Unlisted chemistry procedure

Possibly Covered

81552 Oncology (uveal melanoma), mRNA, gene expression profiling by real-hyphentime RT-hyphenPCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-hyphenfixed paraffin-hyphenembedded tissue, algorithm reported as risk of metastasis **(DecisionDx-UM)**

HCPCS Codes

No applicable codes

ICD-10 Codes

C69.30-C69.42 Malignant neoplasm of choroid and ciliary body (localized uveal melanoma)

References:

1. American Cancer Society (2020) "About Melanoma Skin Cancer" Last revised August 14, 2019. Accessed: August 15, 2022. Available at: www.cancer.org
2. Ardakani MN, Thomas C, Robinson C, et al. Detection of copy number variations in melanocytic lesions utilizing array based comparative genomic hybridization. Pathology. 2017 Apr;49(3):285-291.
3. Berger AC, Davidson RS, Poitras JK, et al. Clinical impact of a 31-gene expression profile test for cutaneous melanoma in 156 prospectively and consecutively tested patients. Curr Med Res Opin. 2016 Sep;32(9):1599-604.
4. Bichakjian CK, Halpern AC, Johnson TM, et al. Guidelines of care for the management of primary cutaneous melanoma. J Am Acad Dermatol. 2011; 65:1032-1047.
5. Castle Biosciences, Inc (2020) "DecisionDx•-Melanoma Overview" Accessed August 3, 2020. Available at: https://castlebiosciences.com/products/decisiondx-melanoma/
6. Chang AE, Karnell LH, Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer. Oct 15, 1998; 83(8): 1664-78. PMID 9781962
7. ClinicalTrials.gov. 5 Year Registry Study to Track Clinical Application of DecisionDx-UM Assay Results and Associated Patient Outcomes (CLEAR). Updated January 25, 2018. Accessed August 12, 2020. Available at: https://clinicaltrials.gov/ct2/show/study/NCT02376920
8. Ferris LK, Gerami P, Skelsey MK,et al. Real-world performance and utility of a noninvasive gene expression assay to evaluate melanoma risk in pigmented lesions. Melanoma Res. 2018 Oct;28(5):478-482.
9. Ferris LK, Jansen B, Ho J, et al. Utility of a noninvasive 2-gene molecular assay for cutaneous melanoma and effect on the decision to biopsy. JAMA Dermatol. 2017;153(7):675–680.
10. Gerami P, Alsobrook JP II, Palmer TJ, Robin HS. Development of a novel noninvasvie adhesive patch test for the evaluation of pigmented lesions of the skin. J Am Acad Dermatol. 2014; 71:237-244.

11. Gerami P, Yao Z, Polsky D, et al. Development and validation of a noninvasive 2-gene molecular assay for cutaneous melanoma. J Am Acad Dermatol. 2017; 76(1):114-120.
12. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(6):472-492.
13. Grossman D, Okwundu N, Bartlett EK, Marchetti MA, Othus M, Coit DG, Hartman RI, Leachman SA, Berry EG, Korde L, Lee SJ. Prognostic gene expression profiling in cutaneous melanoma: identifying the knowledge gaps and assessing the clinical benefit. JAMA dermatology. 2020 Sep 1;156(9):1004-11.
14. Hayes, Inc (2020) "DecisionDx-Melanoma". Last review April 24, 2020. Accessed August 8, 2020. Available at: https://evidence.hayesinc.com/report/gte.decision3123
15. Hayes, Inc (2020) "DecisionDx-UM" Last reviewed June 17, 2020. Accessed August 12, 2020. Available at: https://evidence.hayesinc.com/report/gte.decision2107
16. Hsueh EC, DeBloom JR, Lee J, et al. Interim analysis of survival in a prospective, multi-center registry cohort of cutaneous melanoma tested with a prognostic 31-gene expression profile test [published correction appears in J Hematol Oncol. 2017 Oct 5;10 (1):160]. J Hematol Oncol. 2017;10(1):152. Published 2017 Aug 29. doi:10.1186/s13045-017-0520-1
17. Krantz BA, Dave N, Komatsubara KM, Marr BP, Carvajal RD. Uveal melanoma: epidemiology, etiology, and treatment of primary disease. Clin Ophthalmol. 2017;11:279-289.
18. Luo H, Ma C, Shao J, Cao J. Prognostic Implications of Novel Ten-Gene Signature in Uveal Melanoma. Front Oncol. 2020 Oct 30;10:567512.
19. Marchetti MA, Coit DG, Dusza SW, Yu A, McLean L, Hu Y, Nanda JK, Matsoukas K, Mancebo SE, Bartlett EK. Performance of gene expression profile tests for prognosis in patients with localized cutaneous melanoma: a systematic review and meta-analysis. JAMA dermatology. 2020 Sep 1;156(9):953-62.
20. National Cancer Institute (NCI). Intraocular (uveal) melanoma treatment (PDQ®). Updated December 17, 2019. Available at: https://www.cancer.gov/types/eye/hp/intraocular-melanoma-treatment-pdq. Accessed August 8, 2020.
21. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Melanoma: Uveal Version2.2022. See page UM-2A
22. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Melanoma: Cutaneous Version 2.2023. See page ME-C, page 1-8
23. Plasseraud KM, Cook RW, Tsai T, et al. Clinical performance and management outcomes with the DecisionDx-UM gene expression profile test in a prospective multicenter study. J Oncol. 2016;2016::5325762. Epub June 30, 2016. Accessed August 12, 2020. Available at: https://doi.org/10.1155/2016/5325762
24. Plasseraud KM, Wilkinson JK, Oelschlager KM, et al. Gene expression profiling in uveal melanoma: technical reliability and correlation of molecular class with pathologic characteristics. Diagn Pathol. 2017;12(1):59.
25. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. Jan 2018; 68(1): 7-30. PMID 29313949
26. Swetter, SM, Tsao, H, Bichakjian, CK, et al. Guidelines of care for the management of primary cutaneous melanoma. J Am Acad Dermatol. 2019 Jan;80(1):208-50. PMID: 30392755
27. UpToDate (2019). "Tumor, node, metastasis (TNM) staging system and other prognostic factors in cutaneous melanoma". Last reviewed May 8, 2019. Accessed August 5, 2020. Available at: www.uptodate.com
28. Vetto JT, Hsueh EC, Gastman BR, et al. Guidance of sentinel lymph node biopsy decisions in patients with T1-T2 melanoma using gene expression profiling. Future Oncol. 2019;15(11):1207-1217. doi:10.2217/fon-2018-0912
29. Zager JS, Gastman BR, Leachman S, et al. Performance of a prognostic 31-gene expression profile in an independent cohort of 523 cutaneous melanoma patients. BMC Cancer. 2018;18:130.