Gene Expression Profiling for Cutaneous Melanoma

Policy # 00622
Original Effective Date: 08/15/2018
Current Effective Date: 09/13/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers gene expression testing, including but not limited to the Pigmented Lesion Assay, in the evaluation of patients with suspicious pigmented lesions to be **investigational.***

Based on review of available data, the Company considers gene expression testing, including but not limited to the myPath Melanoma test, in the evaluation of patients with melanocytic lesions with indeterminate histopathologic features to be **investigational.***

Based on review of available data, the Company considers gene expression testing, including but not limited to DecisionDx-Melanoma, in the evaluation of patients with cutaneous melanoma for all indications to be **investigational.***

Policy Guidelines

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

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Background/Overview

Cutaneous Melanoma

Cutaneous melanoma accounts for more than 90% of cases of melanoma. For many decades, melanoma incidence was rapidly increasing in the U.S. However, recent estimates have suggested the rise may be slowing. In 2018, more than 90000 new cases of melanoma are expected to be diagnosed, and more than 9,000 people are expected to die of melanoma.

Risk Factors

Exposure to solar ultraviolet radiation is a major risk factor for melanoma. Most melanomas occur on the sun-exposed skin, particularly those areas most susceptible to sunburn. Likewise, features that are associated with an individual's sensitivity to sunlight, such as light skin pigmentation, red or blond hair, blue or green eyes, freckling tendency, and poor tanning ability are well-known risk factors for melanoma. There is also a strong association between high total body nevus counts and melanoma.

Several genes appear to contribute to melanoma predisposition such as tumor suppressor gene *CDKN2A*, melanocortin-1 receptor (*MC1R*) gene, and *BAP1* variants. Individuals with either familial or sporadic melanoma have a two to three times increased risk of developing a subsequent primary melanoma. Several occupational exposures and lifestyle factors, such as body mass index and smoking, have been evaluated as possible risk factors for melanoma.

Gene Expression Profiling

Gene expression profiling (GEP) measures the activity of thousands of genes simultaneously and creates a snapshot of cellular function. Data for GEP are generated by several molecular technologies including DNA microarrays that measures activity relative to previously identified genes and RNA-Seq that directly sequences and quantifies RNA molecules. Clinical applications of GEP include disease diagnosis, disease classification, prediction of drug response, and prognosis.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. The Pigmented Lesion Assay, myPath Melanoma, and

DecisionDx-Melanoma tests are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Rationale/Source

Laboratory tests have been developed that detect the expression of different genes in pigmented lesions or melanoma tumor tissue. Test results may help providers and patients decide whether to biopsy suspicious pigmented lesions, aid in diagnosis lesions with indeterminate histopathologic lesions or determine whether to perform sentinel lymph node biopsy in patients diagnosed with stage I or II cutaneous melanoma. This report summarizes the evidence of 3 tests.

Summary of Evidence

For individuals with suspicious pigmented lesions (based on ABCDE and/or ugly duckling criteria) being considered for biopsy who receive GEP with the DermTech Pigmented Lesion Assay to determine which lesions should proceed to biopsy, the evidence includes observational studies. Relevant outcomes are overall survival, disease-specific survival, validity, and resource utilization. The Pigmented Lesion Assay has 1 clinical validity study with many methodologic and reporting limitations. Therefore, performance characteristics are not well-characterized. Also, the test has not been compared with dermoscopy, another tool frequently used to make biopsy decisions. No direct evidence of clinical utility was identified. Given that the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility through a chain of evidence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have melanocytic lesions with indeterminate histopathologic features who receive GEP with the myPath Melanoma test added to histopathology to aid in the diagnosis of melanoma, the evidence includes observational studies. Relevant outcomes are overall survival, disease-specific survival, test validity, change in disease status, treatment-related morbidity. The myPath test has 1 clinical validity study, which includes long-term follow-up for metastasis as the reference standard. However, it is not clear if the study population included lesions that were indeterminate following histopathology and the study had other methodologic and reporting limitations. Therefore, performance characteristics are not well-characterized. No direct evidence of

clinical utility was identified. Given that the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility through a chain of evidence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with American Joint Committee on Cancer (AJCC) stage I to III cutaneous melanoma who receive GEP with the DecisionDx-Melanoma test to inform management decisions regarding surveillance, the evidence includes retrospective and prospective observational studies. Relevant outcomes are overall survival, disease-specific survival, test validity, change in disease status, resource utilization and treatment-related morbidity. The DecisionDx-Melanoma test has 3 independent clinical validity studies that have reported 5-year recurrence-free survival (RFS) in AJCC stage I or II patients. Gerami et al (2015) reported RFS rates of 37% for DecisionDx class 2 (high-risk) in patients in AJCC stage I and II patients combined. Zager et al (2018) reported RFS rates of 85% (95% confidence interval [CI], 74% to 97%) for DecisionDx class 2 patients in AJCC stage 1 and 55% (95% CI, 44% to 69%) for DecisionDx class 2 in AJCC stage II disease. RFS does not appear to be well-characterized as evidenced by the variation in estimates across studies. This indication is to 'rule-in' patients for enhanced surveillance; therefore, specificity and positive predictive value (PPV) are key performance characteristics. Zager et al (2018) and Greenhaw et al (2018) the specificities were 71% and 87% respectively while the PPV were 48% and 24%, respectively. The PPV suggests that the majority of patients identified as high-risk by the DecisionDx test would not develop metastasis and would be unnecessarily subjected to additional surveillance. Greenhaw et al (2018) also reported that in 219 AJCC stage I patients, 201 had DecisionDx class 1 (low-risk) scores and 18 had DecisionDx class 2 (high-risk) scores. The only metastasis in stage I patients occurred in a patient with a DecisionDx class 1 score. Therefore none of their stage 1 patients benefited from DecisionDx testing but 18 (8%) were incorrectly identified as high-risk for metastasis and could have received unnecessary surveillance. Five-year RFS data are not available for the subgroup of patients for whom a 'rule-out' test would be relevant (class IIB through III). There is no evidence that changes to the frequency and methods for surveillance improve outcomes. Given that the evidence is insufficient to demonstrate test performance and there is no evidence that changes in surveillance improve outcomes, no inferences can be made about clinical utility through a chain of evidence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with AJCC stage I or II cutaneous melanoma who receive GEP with the DecisionDx-Melanoma test to inform management decisions regarding adjuvant therapy, the evidence includes

retrospective and prospective observational studies. Relevant outcomes are overall survival, disease-specific survival, test validity, change in disease status, resource utilization and treatment-related morbidity. The DecisionDx-Melanoma test has 3 independent clinical validity studies that have reported 5-year RFS in AJCC stage I or II patients. Gerami et al (2015) reported RFS rates of 37% for DecisionDx class 2 (high-risk) in patients in AJCC stage I and II patients combined. Zager et al (2018) reported RFS rates of 85% (95% CI, 74% to 97%) for DecisionDx class 2 patients in AJCC stage 1 and 55% (95% CI, 44% to 69%) for DecisionDx class 2 in AJCC stage II disease. RFS does not appear to be well-characterized as evidenced by the variation in estimates across studies. This indication is to 'rule-in' patients for adjuvant therapy; therefore, specificity and PPV are key performance characteristics. Zager et al (2018) and Greenhaw et al (2018) the specificities were 71% and 87% respectively while the PPV were 48% and 24%, respectively. The PPV suggests that the majority of patients identified as high-risk by the DecisionDx test would not develop metastasis and would be unnecessarily subjected to additional treatment. Greenhaw et al (2018) also reported that in 219 AJCC stage I patients, 201 had DecisionDx class 1 (low-risk) scores and 18 had DecisionDx class 2 (high-risk) scores. The only metastasis in stage I patients occurred in a patient with a DecisionDx class 1 score. Therefore none of their stage 1 patients benefited from DecisionDx testing but 18 (8%) were incorrectly identified as high-risk for metastasis and could have received unnecessary treatment. There is no evidence that adjuvant therapy improves outcomes in these patients. Given that the evidence is insufficient to demonstrate test performance and there is no evidence that adjuvant therapy improves outcomes, no inferences can be made about clinical utility through a chain of evidence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with stage I or II cutaneous melanoma with clinically negative sentinel node basins who are being considered for sentinel lymph node (SLN) biopsy who receive GEP with the DecisionDx-Melanoma test to determine whether to perform SLN biopsy, the evidence includes retrospective observational studies. Relevant outcomes are overall survival, disease-specific survival, test validity, change in disease status, resource utilization and treatment-related morbidity. The DecisionDx-Melanoma test has 3 independent clinical validity studies that have reported 5-year RFS in AJCC stage I or II patients. Gerami et al (2015) reported RFS rates of 98% in DecisionDx class 1 (low-risk) without CIs, in AJCC stage I or II patients. Zager et al (2017) reported RFS rates of 96% (95% CI, 94% to 99%) for DecisionDx class 1 in patients with AJCC stage I disease; they also reported RFS rates of 74% (95% CI, 60% to 91%) for DecisionDx class 1 in patients with AJCC stage II disease. Although CIs were not available for the first study, RFS does not appear to be well-

characterized as evidenced by the variation in estimates across studies. Zager et al (2017) also reported that in 56 patients who were DecisionDx class 1 (low-risk) but SLN biopsy-positive, 22 recurrences (39%) occurred over 5 years. If the DecisionDx test were used as a triage for SLN biopsy, these patients would not undergo SLN biopsy and would likely not receive adjuvant therapy, which has shown to be effective at prolonging time to recurrence in node-positive patients. Data on 5-year RFS is not available for the target population (Class 1A patients ≤55 years old who have tumors less than 2 mm deep [T1 to T2]) outside of the retrospective cohort that was used to identify the target population. No direct evidence of clinical utility was identified. Given that the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility through a chain of evidence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines (v.2.2021) for melanoma made the following statements on use of gene expression profiling.

The guidelines state the following regarding diagnostic testing for indeterminate melanocytic neoplasms following histopathology: "Melanocytic neoplasms of uncertain biologic potential present a unique challenge to pathologists and treating clinicians. Ancillary methods to aid in benign versus malignant differentiation include molecular cytogenetics (eg, comparative genomic hybridization [CGH]), fluorescence in situ hybridization [FISH]), GEP, next generation sequencing (NGS), and immunohistochemistry (IHC), among others. While limited report on the intermediate

category of melanocytic neoplasia show evolutionary pathogenic genetic alteration during melanoma progression, there are insufficient data from histologically ambiguous melanocytic neoplasms."

The guidelines state the following regarding prognostic testing:

- 'The use of GEP testing according to specific AJCC-8 melanoma stage (before or after sentinel lymph node biopsy [SLNB]) requires further prospective investigation in large, contemporary data sets of unselected patients. Prognostic GEP testing to differentiate melanomas at low versus high risk for metastasis should not replace pathologic staging procedures. Moreover, since there is a low probability of metastasis in stage I melanoma and a higher proportion of false-positive results, GEP testing should not guide clinical decision-making in this subgroup."
- "Commercially available 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 that incorporate patient sex, age, tumor location and thickness, …. 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 outcomes, though not superior to Breslow thickness or SLN status. It remains unclear whether available GEP platforms are reliably predictive of outcome across the risk spectrum of melanoma. Prospective validation studies (as have been performed in breast cancer) are required to more accurately 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.'

American Academy of Dermatology

In 2019, the American Academy of Dermatology published guidelines of care for the management of primary cutaneous melanoma. The guidelines state the following regarding GEP tests:

- Regarding diagnostic GEP tests:
    - "Diagnostic molecular techniques are still largely investigative and may be appropriate as ancillary tests in equivocal melanocytic neoplasms, but they are not

recommended for routine diagnostic use in CM [cutaneous melanoma]. These include comparative genomic hybridization, fluorescence in situ hybridization, GEP, and (potentially) next-generation sequencing."
    - "Ancillary diagnostic molecular techniques (eg, CGH, FISH, GEP) may be used for equivocal melanocytic neoplasms."
- Regarding prognostic GEP tests:
    - "...there is also insufficient evidence of benefit to recommend routine use of currently available prognostic molecular tests, including GEP, to provide more accurate prognosis beyond currently known clinicopathologic factors" (Strength of evidence: C, Level of evidence II/III)
    - "Going forward, GEP assays should be tested against all known histopathologic prognostic factors and contemporary eighth edition of AJCC CM staging to assess their additive value in prognostication."
    - "Routine molecular testing, including GEP, for prognostication is discouraged until better use criteria are defined. The application of molecular information for clinical management (eg, sentinel lymph node eligibility, follow-up, and/or therapeutic choice) is not recommended outside of a clinical study or trial."

In 2019, the American Academy of Dermatology updated their Choosing Wisely recommendation that physicians not perform SLN biopsy or other diagnostic tests for the evaluation of early, thin melanoma because they do not improve survival. The Academy noted that early, thin melanoma (melanoma in situ, T1a melanoma or T1b melanoma $\leq$ 0.5 mm) has a very low risk of the cancer spreading to the lymph nodes or other parts of the body and a 97% 5-year survival rate.

National Society for Cutaneous Medicine
In 2019, the National Society for Cutaneous Medicine published appropriate use criteria for the integration of diagnostic and prognostic gene expression profile assays for management of cutaneous melanoma. The criteria were developed with "unrestricted educational grants from related companies involved with these technologies". The majority of the panel members were consultants or advisors for Castle BioSciences or Myriad. The criteria were consensus-based using a modified Delphi approach. Numerous recommendations were made for each of the tests reviewed here. Some of the recommendations are as follows:

- Using Pigmented Lesion Assay test for patients with atypical lesions requiring assessment beyond visual inspection to help in selection for biopsy (B = Inconsistent or limited quality patient-oriented evidence)
- Using myPath for differentiation of a nevus from melanoma in an adult patient when the morphologic findings are ambiguous by light microscopic parameters (A = Consistent, good-quality patient-oriented evidence)
- Using DecisionDx by integrating results into the decision to adjust follow up regimens or to assess need for imaging (B = Inconsistent or limited quality patient-oriented evidence)
- Using DecisionDx by integrating results into subsequent management of patients:
  - Who are sentinel node negative (A = Consistent, good-quality patient-oriented evidence)
  - Who are in AJCC "low risk" categories: (Thin (<1mm), Stage I-IIA, SLNBx-) (B= Inconsistent or limited quality patient-oriented evidence)
- Using DecisionDx by integrating 31-GEP results as a criteria for inclusion in a chemotherapy regimen (C = Consensus, disease-oriented evidence, usual practice, expert opinion, or case series)

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02355574[a]	An Ongoing, 5-year Post Market Study to Track Clinical Application of DecisionDx-Melanoma GEP	1672	Jun 2024

	Assay Results and the Impact on Patient Outcomes and Health Economics (INTEGRATE)		
NCT02355587[a]	An Open, 5-year Registry Study to Track Clinical Application of DecisionDx-Melanoma Gene Expression Profile Assay Results and Associated Patient Outcomes	5000	Feb 2024

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Policy History

Original Effective Date: 08/15/2018
Current Effective Date: 09/13/2021
08/09/2018 Medical Policy Committee review
08/15/2018 Medical Policy Implementation Committee approval. New policy.
08/01/2019 Medical Policy Committee review
08/14/2019 Medical Policy Implementation Committee approval. No change to coverage.
08/06/2020 Medical Policy Committee review
08/12/2020 Medical Policy Implementation Committee approval. No change to coverage.
12/11/2020 Coding update
08/05/2021 Medical Policy Committee review
08/11/2021 Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date: 08/2022

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2020 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0089U, 0090U, 81401, 81479, 81599, 84999 Code added eff 1/1/2021: 81529
HCPCS	No codes
ICD-10 Diagnosis	C43.0-C43.9, C4A.0-C4A.9, C44.0-C44.99, D03.0-D03.9, D04.0-D04.9, L81.0-L81.9, Z12.83, Z80.8

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

3. Reference to federal regulations.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.