Gene Expression Profiling for Cutaneous Melanoma

Policy # 00622
Original Effective Date: 08/15/2018
Current Effective Date: 09/14/2020

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.

Gene Expression Profiling for Cutaneous Melanoma

Policy # 00622
Original Effective Date: 08/15/2018
Current Effective Date: 09/14/2020

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

GEP measures the activity of thousands 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

Gene Expression Profiling for Cutaneous Melanoma

Policy # 00622
Original Effective Date: 08/15/2018
Current Effective Date: 09/14/2020

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. Food and Drug Administration 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 three tests.

For individuals with suspicious pigmented lesions (based on ABCDE and/or ugly duckling criteria) being considered for biopsy who receive gene expression profiling (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 one 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 the effects of the technology on health outcomes.

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 one 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 the effects of the technology on health outcomes.

For individuals with American Joint Committee on Cancer (AJCC) stage I or II cutaneous melanoma who receive GEP with the DecisionDx-Melanoma test to inform management decisions regarding enhanced 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 three independent clinical validity studies that have reported five-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 the effects of the technology on health outcomes.

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 three independent clinical validity studies that have reported five-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 the effects of the technology on health outcomes.

For individuals with cutaneous melanoma with clinically negative sentinel node basins who are being considered for sentinel lymph node biopsy (SLNB) who receive GEP with the DecisionDx-Melanoma test to determine whether to perform SLNB), 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 three independent clinical validity studies that have reported five-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 SLNB-positive, 22 recurrences (39%) occurred over 5 years. If the DecisionDx test were used as a triage for SLNB, these patients would not undergo SLNB and would likely not receive adjuvant therapy, which has shown to be effective at prolonging time to recurrence in node-positive patients. Data on five-year RFS is not available for the target population (Class 1A patients ≤55 years old who have tumors less than 2 mm deep [T1-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 the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines (v.2.2020) 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]), gene expression profiling (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:

- 'Prognostic gene expression profiling (GEP) to differentiate melanomas at low versus high risk for metastasis may provide information on individual risk of recurrence, as an adjunct to standard AJCC staging. However, the currently available prognostic molecular techniques should not replace pathologic staging procedures and the use of GEP testing,

according to specific melanoma stage (before or after sentinel lymph node biopsy [SLNB]) requires further prospective investigation in large, contemporary data sets of unselected patients.'

- 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 this GEP profile is reliably predictive of outcome… 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. These include comparative genomic hybridization, fluorescence in situ hybridization, gene expression profiling (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."

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 PLA 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 31GEP 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 Gene Expression Profile (GEP) Assay Results and the Impact on Patient Outcomes and Health Economics	1672	Jun 2024
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.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Gene Expression Profiling for Cutaneous Melanoma", 2.04.146, 6:2020.
2. 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
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. Jan 2018; 68(1): 7-30. PMID 29313949
4. Gilchrest BA, Eller MS, Geller AC, et al. The pathogenesis of melanoma induced by ultraviolet radiation. N Engl J Med. Apr 29 1999; 340(17): 1341-8. PMID 10219070
5. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. Eur J Cancer. Sep 2005; 41(14): 2040-59. PMID 16125929
6. Caini S, Gandini S, Sera F, et al. Meta-analysis of risk factors for cutaneous melanoma according to anatomical site and clinico-pathological variant. Eur J Cancer. Nov 2009; 45(17): 3054-63. PMID 19545997
7. Goldstein AM, Chan M, Harland M, et al. Features associated with germline CDKN2A mutations: a GenoMEL study of melanoma-prone families from three continents. J Med Genet. Feb 2007; 44(2): 99-106. PMID 16905682
8. Wendt J, Rauscher S, Burgstaller-Muehlbacher S, et al. Human Determinants and the Role of Melanocortin-1 Receptor Variants in Melanoma Risk Independent of UV Radiation Exposure. JAMA Dermatol. Jul 01 2016; 152(7): 776-82. PMID 27050141
9. Wiesner T, Obenauf AC, Murali R, et al. Germline mutations in BAP1 predispose to melanocytic tumors. Nat Genet. Aug 28 2011; 43(10): 1018-21. PMID 21874003
10. Chen T, Fallah M, Forsti A, et al. Risk of Next Melanoma in Patients With Familial and Sporadic Melanoma by Number of Previous Melanomas. JAMA Dermatol. Jun 2015; 151(6): 607-15. PMID 25671687
11. Jiang AJ, Rambhatla PV, Eide MJ. Socioeconomic and lifestyle factors and melanoma: a systematic review. Br J Dermatol. Apr 2015; 172(4): 885-915. PMID 25354495
12. Abbasi NR, Shaw HM, Rigel DS, et al. Early diagnosis of cutaneous melanoma: revisiting the ABCD criteria. JAMA. Dec 08 2004; 292(22): 2771-6. PMID 15585738
13. Grob JJ, Bonerandi JJ. The 'ugly duckling' sign: identification of the common characteristics of nevi in an individual as a basis for melanoma screening. Arch Dermatol. Jan 1998; 134(1): 103-4. PMID 9449921
14. Wilson RL, Yentzer BA, Isom SP, et al. How good are US dermatologists at discriminating skin cancers? A number-needed-to-treat analysis. J Dermatolog Treat. Feb 2012; 23(1): 65-9. PMID 21756146

15. National Center for Biotechnology Information. PRAME preferentially expressed antigen in melanoma. 2018; https://www.ncbi.nlm.nih.gov/gene/23532.
16. DermTech. Pigmented Lesion Assay: Non-invasive gene expression analysis of pigmented skin lesions. Performance and Development Notes. 2015; http://dermtech.com/wp-content/uploads/2015/10/White-Paper- DermTech-Melanoma-Assay-.pdf.
17. Wachsman W, Morhenn V, Palmer T, et al. Noninvasive genomic detection of melanoma. Br J Dermatol. Apr 2011; 164(4): 797-806. PMID 21294715
18. Gerami P, Alsobrook JP, Palmer TJ, et al. Development of a novel noninvasive adhesive patch test for the evaluation of pigmented lesions of the skin. J Am Acad Dermatol. Aug 2014; 71(2): 237-44. PMID 24906614
19. 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. Jan 2017; 76(1): 114-120.e2. PMID 27707590
20. Vestergaard ME, Macaskill P, Holt PE, et al. Dermoscopy compared with naked eye examination for the diagnosis of primary melanoma: a meta-analysis of studies performed in a clinical setting. Br J Dermatol. Sep 2008; 159(3): 669-76. PMID 18616769
21. Murzaku EC, Hayan S, Rao BK. Methods and rates of dermoscopy usage: a cross-sectional survey of US dermatologists stratified by years in practice. J Am Acad Dermatol. Aug 2014; 71(2): 393-5. PMID 25037790
22. Engasser HC, Warshaw EM. Dermatoscopy use by US dermatologists: a cross-sectional survey. J Am Acad Dermatol. Sep 2010; 63(3): 412-9, 419.e1-2. PMID 20619490
23. Bossuyt PM, Irwig L, Craig J, et al. Comparative accuracy: assessing new tests against existing diagnostic pathways. BMJ. May 06 2006; 332(7549): 1089-92. PMID 16675820
24. 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. Oct 2018; 28(5): 478-482. PMID 30004988
25. 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. Jul 01 2017; 153(7): 675-680. PMID 28445578
26. Myriad. n.d. Understanding the myPath Melanoma Results; https://mypathmelanoma.com/about-mypath- melanoma/understanding-the-mypath-melanoma-results/.

27. Clarke LE, Warf MB, Flake DD, et al. Clinical validation of a gene expression signature that differentiates benign nevi from malignant melanoma. J Cutan Pathol. Apr 2015; 42(4): 244-52. PMID 25727210
28. Clarke LE, Flake DD, Busam K, et al. An independent validation of a gene expression signature to differentiate malignant melanoma from benign melanocytic nevi. Cancer. Feb 15 2017; 123(4): 617-628. PMID 27768230
29. Reimann JDR, Salim S, Velazquez EF, et al. Comparison of melanoma gene expression score with histopathology, fluorescence in situ hybridization, and SNP array for the classification of melanocytic neoplasms. Mod Pathol. Nov 2018; 31(11): 1733-1743. PMID 29955141
30. Gaiser T, Kutzner H, Palmedo G, et al. Classifying ambiguous melanocytic lesions with FISH and correlation with clinical long-term follow up. Mod Pathol. Mar 2010; 23(3): 413-9. PMID 20081813
31. Vergier B, Prochazkova-Carlotti M, de la Fouchardiere A, et al. Fluorescence in situ hybridization, a diagnostic aid in ambiguous melanocytic tumors: European study of 113 cases. Mod Pathol. May 2011; 24(5): 613-23. PMID 21151100
32. Ko JS, Clarke LE, Minca EC, et al. Correlation of melanoma gene expression score with clinical outcomes on a series of melanocytic lesions. Hum Pathol. Apr 2019; 86: 213-221. PMID 30566894
33. Clarke LE, Pimentel JD, Zalaznick H, et al. Gene expression signature as an ancillary method in the diagnosis of desmoplastic melanoma. Hum Pathol. Dec 2017; 70: 113-120. PMID 29079183
34. Minca EC, Al-Rohil RN, Wang M, et al. Comparison between melanoma gene expression score and fluorescence in situ hybridization for the classification of melanocytic lesions. Mod Pathol. Aug 2016; 29(8): 832-43. PMID 27174586
35. Ko JS, Matharoo-Ball B, Billings SD, et al. Diagnostic Distinction of Malignant Melanoma and Benign Nevi by a Gene Expression Signature and Correlation to Clinical Outcomes. Cancer Epidemiol Biomarkers Prev. Jul 2017; 26(7): 1107-1113. PMID 28377414
36. Cockerell C, Tschen J, Billings SD, et al. The influence of a gene-expression signature on the treatment of diagnostically challenging melanocytic lesions. Per Med. Mar 2017; 14(2): 123-130. PMID 28757886
37. Cockerell CJ, Tschen J, Evans B, et al. The influence of a gene expression signature on the diagnosis and recommended treatment of melanocytic tumors by dermatopathologists. Medicine (Baltimore). Oct 2016; 95(40): e4887. PMID 27749545
38. Gershenwald JES, R.A.; Hess, K.R.; et al. Melanoma of the Skin. Chicago, IL: American Joint Committee on Cancer; 2017.

39. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy. N Engl J Med. Nov 10 2016; 375(19): 1845-1855. PMID 27717298
40. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. N Engl J Med. Nov 09 2017; 377(19): 1824-1835. PMID 28891423
41. Long GV, Hauschild A, Santinami M, et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. N Engl J Med. Nov 09 2017; 377(19): 1813-1823. PMID 28891408
42. Gerami P, Cook RW, Wilkinson J, et al. Development of a prognostic genetic signature to predict the metastatic risk associated with cutaneous melanoma. Clin Cancer Res. Jan 01 2015; 21(1): 175-83. PMID 25564571
43. 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. Feb 05 2018; 18(1): 130. PMID 29402264
44. Wrightson WR, Wong SL, Edwards MJ, et al. Complications associated with sentinel lymph node biopsy for melanoma. Ann Surg Oncol. Jul 2003; 10(6): 676-80. PMID 12839853
45. Soong SJ, Ding S, Coit DG, et al. AJCC: Individualized melanoma patient outcome prediction tools. n.d.; http://www.melanomaprognosis.net/.
46. Callender GG, Gershenwald JE, Egger ME, et al. A novel and accurate computer model of melanoma prognosis for patients staged by sentinel lymph node biopsy: comparison with the American Joint Committee on Cancer model. J Am Coll Surg. Apr 2012; 214(4): 608-17; discussion 617-9. PMID 22342785
47. Dicker TJ, Kavanagh GM, Herd RM, et al. A rational approach to melanoma follow-up in patients with primary cutaneous melanoma. Scottish Melanoma Group. Br J Dermatol. Feb 1999; 140(2): 249-54. PMID 10233217
48. Garbe C, Paul A, Kohler-Spath H, et al. Prospective evaluation of a follow-up schedule in cutaneous melanoma patients: recommendations for an effective follow-up strategy. J Clin Oncol. Feb 01 2003; 21(3): 520-9. PMID 12560444
49. Faries MB, Steen S, Ye X, et al. Late recurrence in melanoma: clinical implications of lost dormancy. J Am Coll Surg. Jul 2013; 217(1): 27-34; discussion 34-6. PMID 23643694
50. 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. J Hematol Oncol. Aug 29 2017; 10(1): 152. PMID 28851416

51. Podlipnik S, Carrera C, Boada A, et al. Early outcome of a 31-gene expression profile test in 86 AJCC stage IB-II melanoma patients. A prospective multicentre cohort study. J Eur Acad Dermatol Venereol. May 2019; 33(5): 857-862. PMID 30702163
52. Gastman BR, Gerami P, Kurley SJ, et al. Identification of patients at risk of metastasis using a prognostic 31-gene expression profile in subpopulations of melanoma patients with favorable outcomes by standard criteria. J Am Acad Dermatol. Jan 2019; 80(1): 149-157.e4. PMID 30081113
53. Gastman BR, Zager JS, Messina JL, et al. Performance of a 31-gene expression profile test in cutaneous melanomas of the head and neck. Head Neck. Apr 2019; 41(4): 871-879. PMID 30694001
54. 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. Apr 2019; 15(11): 1207-1217. PMID 30691297
55. Marks, Etan et al. Establishing an evidence-based decision point for clinical use of the 31-gene expression profile test in cutaneous melanoma. SKIN The Journal of Cutaneous Medicine, [S.l.], v. 3, n. 4, p. 239-249, july 2019. ISSN 2574-1624. Available at: <https://jofskin.org/index.php/skin/article/view/628>. doi:https://doi.org/10.25251/skin.3.4.2.
56. Greenhaw BN, Zitelli JA, Brodland DG. Estimation of Prognosis in Invasive Cutaneous Melanoma: An Independent Study of the Accuracy of a Gene Expression Profile Test. Dermatol Surg. Dec 2018; 44(12): 1494-1500. PMID 29994951
57. Keller J, Schwartz TL, Lizalek JM, et al. Prospective validation of the prognostic 31-gene expression profiling test in primary cutaneous melanoma. Cancer Med. May 2019; 8(5): 2205-2212. PMID 30950242
58. Gerami P, Cook RW, Russell MC, et al. Gene expression profiling for molecular staging of cutaneous melanoma in patients undergoing sentinel lymph node biopsy. J Am Acad Dermatol. May 2015; 72(5): 780-5.e3. PMID 25748297
59. Ferris LK, Farberg AS, Middlebrook B, et al. Identification of high-risk cutaneous melanoma tumors is improved when combining the online American Joint Committee on Cancer Individualized Melanoma Patient Outcome Prediction Tool with a 31-gene expression profile-based classification. J Am Acad Dermatol. May 2017; 76(5): 818-825.e3. PMID 28110997
60. 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. Sep 2016; 32(9): 1599-604. PMID 27210115

61. Farberg AS, Glazer AM, White R, et al. Impact of a 31-gene Expression Profiling Test for Cutaneous Melanoma on Dermatologists' Clinical Management Decisions. J Drugs Dermatol. May 01 2017; 16(5): 428-431. PMID 28628677
62. Schuitevoerder D, Heath M, Cook RW, et al. Impact of Gene Expression Profiling on Decision-Making in Clinically Node Negative Melanoma Patients after Surgical Staging. J Drugs Dermatol. Feb 01 2018; 17(2): 196-199. PMID 29462228
63. Dillon LD, Gadzia JE, Davidson RS, et al. Prospective, multicenter clinical impact evaluation of a 31-gene expression profile test for management of melanoma patients. Skin. 2018;2(2):111-121.
64. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Cutaneous Melanoma. Version 2.2020.
65. Swetter SM, Tsao H, Bichakjian CK, et al. Guidelines of care for the management of primary cutaneous melanoma. J Am Acad Dermatol. Jan 2019; 80(1): 208-250. PMID 30392755
66. Berman, et.al. Appropriate Use Criteria for the Integration of Diagnostic and Prognostic Gene Expression Profile Assays into the Management of Cutaneous Malignant Melanoma: An Expert Panel Consensus-Based Modified Delphi Process Assessment. SKIN. 2019; 3(5):291-298.

Policy History

Original Effective Date: 08/15/2018
Current Effective Date: 09/14/2020

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

Next Scheduled Review Date: 08/2021

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 2019 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.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

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.