Medical Coverage Policy | Gene Expression Profiling for Cutaneous Melanoma

EFFECTIVE DATE: 10|01|2018
POLICY LAST UPDATED: 08|24|2021

OVERVIEW

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 of lesions with indeterminate histopathologic findings or determine whether to perform sentinel lymph node biopsy in patients diagnosed with stage I or II cutaneous melanoma.

The following tests are addressed in this policy:

- DecisionDx-Melanoma (Castle Biosciences)
- Pigmented Lesion Assay (DermTech)
- myPath Melanoma (Myriad)

MEDICAL CRITERIA

Medicare Advantage Plans

Pigmented Lesion Assay (PLA) – 0089U

The PLA may be considered medically necessary when all the following criteria are met:

- Melanocytic skin lesions with one or more clinical or historical characteristics suggestive of melanoma, including one or more ABCDE criteria (outlined below) when a clinician trained in the clinical diagnosis of skin cancer is considering the need for biopsy to rule out melanoma:
  - Asymmetry
  - Border
  - Color
  - Diameter
  - Evolving
- Primary melanocytic skin lesions between 5mm and 19mm
- Lesions where the skin is intact (i.e. non-ulcerated or non-bleeding lesions)
- Lesions that do not contain a scar or were previously biopsied
- Lesions not located in areas of psoriasis, eczema or similar skin conditions
- Lesions not clinically diagnosed as melanoma
- Lesions in areas other than palms of hands, soles of feet, nails, mucous membranes and hair covered areas that cannot be trimmed

myPath Melanoma – 0090U

myPath Melanoma may be considered medically necessary for the diagnosis or exclusion of melanoma from a biopsy when all the following criteria are met:

- The test is ordered by a board-certified dermatopathologist and;
- The specimen is a primary cutaneous melanocytic neoplasm for which the diagnosis is equivocal/uncertain (i.e. clear distinction between benign or malignant cannot be achieved using clinical and/or histopathological features alone) and;
- The patient may be subjected to additional intervention, such as re-excision and/or sentinel lymph node biopsy, as a result of the diagnostic uncertainty.

Commercial Products
Not applicable

PRIOR AUTHORIZATION

Medicare Advantage Plans
Prior authorization is required for the following tests:

- Pigmented Lesion Assay
- myPath Melanoma

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

POLICY STATEMENT

Medicare Advantage Plans
The following tests may be considered medically necessary when the medical criteria above are met:

- Pigmented Lesion Assay
- myPath Melanoma

The following test is not covered as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome:

- DecisionDx-Melanoma

Commercial Products
The following tests are not medically necessary as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome:

- DecisionDx-Melanoma
- Pigmented Lesion Assay
- myPath Melanoma

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable laboratory and not medically necessary/not covered benefits/coverage.

BACKGROUND

CUTANEOUS MELANOMA
Cutaneous melanoma accounts for more than 90% of cases of melanoma. For many decades, melanoma incidence was rapidly increasing in the United States. However, recent estimates have suggested the rise may be slowing. In 2018, more than 90,000 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 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 2 to 3 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)
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 measure 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.

Pigmented Lesion Assay (PLA)
Pigmented Lesion Assay is a gene expression test using samples collected via adhesive patches provides a non-invasive alternative to the surgical biopsy pathway in the assessment of pigmented skin lesions. The test is positive if LINC00518 and/or PRAME (two genes known to be overexpressed in melanoma) are detected. The PLA is based on a platform technology for non-invasive genomic testing of the skin that allows the analysis of samples collected with an adhesive patch. Four patches are placed on a lesion. For each patch, the margin of the lesion is outlined by the clinician. This outlined tissue is dissected away from the surrounding tissue by the processing laboratory, and RNA is extracted only from the lesional tissue. In contrast to histopathologic sectioning, the adhesive patch method of tissue sampling allows the collection of tissue from the entire the lesion in the plane of the skin surface. Further, genomic information obtained by adhesive patch sampling of the stratum corneum contains information from deeper epidermal cells.

The PLA should not be used on clinically obvious melanoma. It is not intended to be used as a screening test in patients without melanocytic skin lesions. It is also not covered as an adjunctive test in lesions that are considered to already warrant a biopsy. The PLA is a decision tool for atypical melanocytic lesions prior to the decision to biopsy. The PLA result is one element of the overall clinical assessment and should be used in combination with clinical and historical signs of melanoma to obtain additional information prior to a decision to biopsy.

Commercial Products
For individuals with suspicious pigmented lesions (based on ABCDE and/or ugly duckling criteria) being considered for biopsy who receive gene expression profiling 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, test accuracy and 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.

myPath Melanoma
The Myriad myPath Melanoma assay is a 23-gene expression signature developed to provide an objective, reproducible, and accurate adjunctive method for differentiating malignant melanoma from benign nevi. The

test is intended for use by dermatopathologists confronting primary cutaneous melanocytic neoplasms for which the diagnosis of malignant melanoma versus benign nevus is equivocal / uncertain (i.e. a clear distinction between benign or malignant cannot be achieved using clinical and / or histopathological features alone). Use of the test in these cases increases definitive diagnoses, and evidence suggests it may reduce unnecessary procedures in benign lesions.

The myPath Melanoma test quantifies the expression of 23 genes by quantitative RT-PCR. Fourteen of the 23 genes are known to be over-expressed by malignant melanomas relative to benign nevi. The remaining nine are stably expressed reference genes which allow correction for sample-to-sample variations in RT-PCR efficiency and errors in sample quantification (normalization). The signature genes represent three distinct pathways that contribute to melanoma pathogenesis, including aspects of melanocyte differentiation as well as characteristics of the tumor microenvironment such as cell-cell signaling and tumor-induced host immune responses. The test uses five to seven standard-thickness (4-5 μm) sections taken from the routinely processed formalin-fixed paraffin-embedded (FFPE) tissue of the existing biopsy specimen, allowing its integration into routine clinical practice and its use even in small, early-stage lesions.

The quantified expression of all 23 genes is combined algorithmically and reported as a single numerical score. That number (the myPath Melanoma 'score'), is plotted on a scale that depicts the entire range of scores observed in clinical validation studies. Physicians receive a report showing this single numerical score and the corresponding classification: 'likely malignant', 'likely benign', or 'indeterminate'.

Commercial Products
For individuals who have melanocytic lesions with indeterminate histopathologic features who receive gene expression profiling 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 accuracy and validity, change in disease status, treatment-related morbidity. The myPath test has 1 clinical validity study, which includes long-term follow-up to establish the clinical diagnosis 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.

DecisionDx-Melanoma
The DecisionDx test measures expression of 31 genes using quantitative reverse-transcription polymerase chain reaction. The test includes 28 prognostic gene targets and 3 endogenous control genes. The test is performed on standard tissue sections from an existing formalin-fixed, paraffin-embedded biopsy or wide local excision specimen. The DecisionDx test report provides a 'class' which stratifies tumors as class 1 or class 2. According to the sample report available on the manufacturer website: "The DecisonDx-Melanoma algorithm generates a value between 0 and 1 with a crossover point of 0.5. Subclassification (A or B) is based on proximity of this value to the crossover point."

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 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 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 that the technology results in an improvement in the net health outcome.

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 that the technology results in an improvement in the net health outcome.

CODING

The following CPT code is not covered for Medicare Advantage Plans and not medically necessary for Commercial Products:
This code can be used for DecisionDx-Melanoma:
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 (New Code Effective 1/1/21)

The following CPT codes are covered for Medicare Advantage Plans when medical criteria above are met and are not medically necessary for Commercial Products:

This code can be used for Pigmented Lesion Assay (PLA):
0089U Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es)

This code can be used for myPath Melanoma:
0090U Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical result (ie, benign, intermediate, malignant) (Revised text 1/01/2022)

RELATED POLICIES

Genetic Testing Services
Proprietary Laboratory Analyses (PLA)

PUBLISHED

Provider Update, October 2021
Provider Update, November 2020
Provider Update, April 2019
Provider Update, August 2018

REFERENCES

1. Centers for Medicare and Medicaid Services. Local Coverage Determination (LCD): MolDX: Pigmented Lesion Assay (L38151)
2. Centers for Medicare and Medicaid Services. Local Coverage Article: Billing and Coding: MolDX: Pigmented Lesion Assay (A58052)
3. Centers for Medicare and Medicaid Services. Local Coverage Determination (LCD): MolDX: myPath Melanoma Assay (L37881)
4. Centers for Medicare and Medicaid Services. Local Coverage Article: Billing and Coding: MolDX: myPath Melanoma Assay (A57627)
5. 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
6. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. Jan 2018; 68(1): 7-30. PMID 29313949
7. 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
8. 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

9. 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
10. 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
11. 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
12. 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
13. 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
14. 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
15. 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
16. 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
17. 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
18. National Center for Biotechnology Information. PRAME preferentially expressed antigen in melanoma. 2021; https://www.ncbi.nlm.nih.gov/gene/23532. Accessed March 29, 2021.
19. 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. Accessed March 29, 2021.
20. Wachsman W, Morhenn V, Palmer T, et al. Noninvasive genomic detection of melanoma. Br J Dermatol. Apr 2011; 164(4): 797-806. PMID 21294715
21. 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
22. 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
23. 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
24. 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
25. 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
26. 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
27. 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
28. 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

29. Myriad. n.d. Understanding the myPath Melanoma Results; https://mypathmelanoma.com/about-mypath- melanoma/understanding-the-mypath-melanoma-results/. Accessed March 29, 2021
30. 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
31. 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
32. 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
33. 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
34. 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
35. 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
36. 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
37. 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
38. 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
39. 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
40. 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
41. Gershenwald JES, R.A.; Hess, K.R.; et al. Melanoma of the Skin. Chicago, IL: American Joint Committee on Cancer; 2017.
42. 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
43. 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
44. 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
45. 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
46. 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
47. 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
48. Soong SJ, Ding S, Coit DG, et al. AJCC: Individualized melanoma patient outcome prediction tools. n.d.; http://www.melanomaprognosis.net/. Accessed March 31, 2021.
49. 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

50. 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
51. 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
52. 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
53. 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
54. 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
55. 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
56. 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
57. 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
58. 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.], July 2019, v. 3, n. 4, p. 239-249.
59. 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
60. 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
61. 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
62. 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
63. 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
64. 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
65. 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
66. 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.
67. Hyams DM, Covington KR, Johnson CE, et al. Integrating the melanoma 31-gene expression profile test with surgical oncology practice within national guideline and staging recommendations. Future Oncol. Feb 2021; 17(5): 517-527. PMID 33021104
68. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Cutaneous Melanoma. Version 2.2021.

https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf.Accessed March 29, 2021.
69. 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
70. American Academy of Dermatology. Choosing Wisely. 2019. https://www.choosingwisely.org/clinician-lists/american-academy-dermatology-sentinal-lymph-node-biopsy-early-melanoma-evaluation/. Accessed March 29, 2021.
71. 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.