



## FEP Medical Policy Manual

### FEP 2.04.146 Gene Expression Profiling for Cutaneous Melanoma

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**Related Policies:**

None

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## Gene Expression Profiling for Cutaneous Melanoma

### Description

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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 the diagnosis of 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.

#### OBJECTIVE

The objective of this evidence review is to determine whether gene expression profiling improves the net health outcome in individuals with lesions suspicious for melanoma or with melanoma.

## POLICY STATEMENT

Gene expression testing, including but not limited to the Pigmented Lesion Assay, in the evaluation of individuals with suspicious pigmented lesions is considered **investigational**.

Gene expression testing, including but not limited to the myPath Melanoma test, in the evaluation of individuals with melanocytic lesions with indeterminate histopathologic features is considered **investigational**.

Gene expression testing, including but not limited to DecisionDx-Melanoma, in the evaluation of individuals with cutaneous melanoma is considered **investigational** for all indications.

## POLICY GUIDELINES

### Genetic Counseling

Experts recommend formal genetic counseling for individuals 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 individuals; 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.

## BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

## FDA REGULATORY STATUS

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. Food and Drug Administration has chosen not to require any regulatory review of this test.

## RATIONALE

### Summary of Evidence

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 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, and treatment-related morbidity. The myPath test has 2 clinical validity studies including long-term follow-up for metastasis as the reference standard. In 1 study, it is not clear whether the study population included lesions that were indeterminate following histopathology. The second study focused on indeterminate lesions but had limitations including a retrospective design and less than 5-year follow-up in 31% of cases. 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. The 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. In 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. In 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  $\leq 55$  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

### 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.

#### American Academy of Dermatology

In 2019, the American Academy of Dermatology published guidelines of care for the management of primary cutaneous melanoma.<sup>69</sup> The guidelines state the following regarding gene expression profiling (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 [FISH], gene expression profiling (GEP), and (potentially) next-generation sequencing."
  - "Ancillary diagnostic molecular techniques (eg, CGH [comparative genomic hybridization], 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 [American Joint Committee on Cancer] 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."

The American Academy of Dermatology's Choosing Wisely recommendation states that physicians not perform sentinel lymph node (SLN) biopsy or other diagnostic tests for the evaluation of early, thin melanoma because they do not improve survival.<sup>70</sup> The Academy noted that early, thin melanoma (melanoma in situ, T1a melanoma or T1b melanoma  $< 0.5$  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 Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines (v.1.2024 ) for cutaneous melanoma made the following statements on use of GEP: <sup>71</sup>,

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 tests to differentiate benign from malignant melanocytic neoplasms include immunohistochemistry (IHC) and molecular testing via comparative genomic hybridization (CGH), fluorescence in situ hybridization (FISH), gene expression profiling (GEP), single-nucleotide polymorphism (SNP) array, and next-generation sequencing (NGS). These tests may facilitate a more definitive diagnosis and guide therapy in cases that are diagnostically uncertain or controversial by histopathology. Ancillary tests should be used as adjuncts to clinical and expert dermatopathologic examination and therefore be interpreted within the context of these findings."

The guidelines state the following regarding prognostic testing:

- "Currently, there is insufficient evidence to support incorporation of current GEP tests into melanoma care. The use of gene expression profiling (GEP) 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 tests to differentiate melanomas at low versus high risk for metastasis should not replace pathologic staging procedures and are not recommended outside of the context of a clinical study or trial. Moreover, since there is a low probability of metastasis in stage I melanoma and a high proportion of false-positive results using these tests, GEP testing should not guide clinical decision-making in this subgroup. In addition, the likelihood of a positive SLNB may be informed by the use of multivariable nomograms/risk calculators. Ongoing prospective investigation will further inform the use of GEP tests for SLNB risk prediction."
- "Despite commercially available GEP tests being marketed to risk stratify cutaneous melanomas, current GEP platforms do not provide clinically actionable prognostic information when combined or compared with known clinicopathologic factors (eg, sex, age, primary tumor location, thickness, ulceration, mitotic rate, lymphovascular invasion, microsatellites, and/or SLNB status). Furthermore, the clinical utility of these tests to inform treatment recommendations and improve health outcomes by prompting an intervention has not been established."
- "Various studies of prognostic GEP tests testing suggest their role as an independent predictor of worse outcomes. However, GEP studies to date have not demonstrated added benefit beyond comprehensive CP variables, and it remains unclear whether available GEP tests are reliably predictive of outcome across the risk spectrum of melanoma. Validation studies on prospectively collected, independent cohorts (similar to those performed in breast cancer) are necessary to define the clinical utility of molecular prognostic GEP testing as an adjunct to AJCC staging and other known prognostically significant CP variables or as part of the multidisciplinary decision-making process to guide surveillance imaging, SLNB, and adjuvant therapy."
- "Existing and emerging GEP tests and other molecular techniques (ie, circulating tumor DNA tests) should be prospectively compared to determine their clinical utility, including with no-cost, contemporary models that incorporate readily available CP variables. Prospective study of the utility of predictive GEP for SLNB risk, in conjunction with well-established CP factors, is ongoing."

## National Society for Cutaneous Medicine

In 2019, the National Society for Cutaneous Medicine published appropriate use criteria for the integration of diagnostic and prognostic GEP assays for management of cutaneous melanoma.<sup>72</sup> 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 to 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.

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## POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
September 2018	Replace policy	Policy created with a literature review through March 5, 2018. Gene expression testing is considered investigational in the evaluation of patients with suspicious pigmented lesions, patients with melanocytic lesions with indeterminate histopathologic features, and of patients with cutaneous melanoma.
September 2019	Replace policy	Policy updated with literature review through March 20, 2019. References added and removed. Policy statements unchanged.
September 2020	Replace policy	Policy updated with literature review through March 20, 2020; references added. Policy statements unchanged

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.



Date	Action	Description
September 2021	Replace policy	Policy updated with literature review through March 25, 2021; references added. Policy statements unchanged.
September 2022	Replace policy	Policy updated with literature review through April 6, 2022; references added. Policy statement terminology changed from "patients" to "individuals"; intent unchanged.
September 2023	Replace policy	Policy updated with literature review through April 7, 2023; no references added. Policy statements unchanged.
September 2024	Replace policy	Policy updated with literature review through March 21, 2024; no references added. Policy statements unchanged.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.