Gene Expression Profiling for Cutaneous Melanoma

Description

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.

OBJECTIVE

The objective of this evidence review is to determine whether gene expression profiling (GEP) 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 patients with suspicious pigmented lesions is considered investigational.

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

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

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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.

BENEFIT APPLICATION

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.

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

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 GEP with the DermTech PLA to determine which lesions should proceed to biopsy, the evidence includes observational studies. The relevant outcomes are overall survival (OS), disease-specific survival, validity, and resource utilization. The PLA 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. The relevant outcomes are OS, 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

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The relevant outcomes are OS, 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 CI's, 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 patients with AJCC stage I disease; they also reported RFS rates of 74% (95% CI, 60% to 91%) for DecisionDX class 1 patients with AJCC stage II disease. Although CI's 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. 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 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 observational studies. The relevant outcomes are OS, 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% confidence interval CI, 74% to 97%) for DecisionDX class 2 patients in AJCC stage I 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 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 the DecisionDX test would not develop metastasis and would be unnecessarily subjected to additional surveillance. 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 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. The relevant outcomes are OS, 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 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 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 surveillance. 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.

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FEP 2.04.146 Gene Expression Profiling for Cutaneous Melanoma
SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines (v.2.2019) for melanoma made the following statements on use of gene expression profiling:

"While there is interest in newer prognostic molecular techniques such as gene expression profiling to differentiate melanomas at low versus high risk for metastasis, routine (baseline) prognostic genetic testing of primary cutaneous melanoma (before or following sentinel lymph node biopsy) is not recommended outside of a clinical study (trial)."

The guidelines state the following regarding diagnostic testing for indeterminate melanocytic neoplasms following histopathology: "They may be used on a case-by-case basis in ambiguous melanocytic tumors; however, their utility is still under evaluation, and more data are needed before they can be routinely recommended." Specifically regarding the GEP test, the guidelines state that "...long-term follow-up is required to validate the prognostic significance of this test."

The guidelines state the following regarding prognostic testing: "Commercially available GEP tests are marketed as being able to classify cutaneous melanoma into separate categories based on 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, ulceration, mitotic rate, lymphovascular invasion, microsatellites, and SLNB status. Furthermore, the impact of these tests on treatment outcomes or follow-up schedules has not been established."

American Academy of Dermatology


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."

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.
Palmetto GBA, Wisconsin Physicians Service Insurance Corporation, and CGS Administrators, LLC have issued draft noncoverage local coverage determination for the Pigmented Lesion Assay.\textsuperscript{64,65,66} Palmetto GBA has issued a draft local coverage determination for DecisionDx-Melanoma.\textsuperscript{67} The comment period for the draft local coverage determination closes on May 10, 2018. The draft states that the quality of the evidence is "Moderate," the strength of evidence is "Low," and weight of evidence is "Low" and that: "This contractor will cover the DecisionDx-Melanoma test for patients diagnosed with SLNB eligible T1b and T2 tumor who are being considered for SLNB. The DecisionDx-Melanoma assay should not be ordered if a patient and his/her physician do not intend to act upon the test result. Continued coverage is dependent on the publication and/or presentation of additional clinical utility data demonstrating the impact of the test’s use on patient management decisions with (1) 95% or greater DMFS [distant metastasis-free survival] and MSS [melanoma-specific survival] at 3 years in patients directed to no SLNB by the test compared to standard of care, and (2) evidence of higher SLNB positivity in patients selected for this procedure by the test compared to standard of care."

REFERENCES


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

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<tr>
<th>Date</th>
<th>Action</th>
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<tr>
<td>September 2018</td>
<td>Replace policy</td>
<td>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.</td>
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