Protocol

Gene Expression Profiling for Cutaneous Melanoma

(204146)

Medical Benefit		**Effective Date**: 10/01/18	**Next Review Date**: 07/19
Preauthorization	No	**Review Dates**: 07/18	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With suspicious pigmented lesions (based on ABCDE and/or ugly duckling criteria) being considered for biopsy	Interventions of interest are: • Gene expression profiling with the DermTech Pigmented Lesion Assay to determine which lesions should proceed to biopsy	Comparators of interest are: • Dermatology exam and dermoscopy	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Resource utilization
Individuals: • Who have melanocytic lesions with indeter-minate histopathologic features	Interventions of interest are: • Gene expression profiling with the myPath Melanoma test added to histopathology to aid in diagnosis of melanoma	Comparators of interest are: • Histopathology alone • Comparative genomic hybridization added to histopathology • Fluorescence in situ hybridization added to histopathology	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Change in disease status • Treatment-related morbidity
Individuals: • With American Joint Committee on Cancer stage I or II cutaneous melanoma	Interventions of interest are: • Gene expression profiling with the DecisionDx-Melanoma test to determine whether to perform sentinel lymph node biopsy	Comparators of interest are: • Sentinel lymph node biopsy • Prognostic tools	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Change in disease status • Resource utilization • Treatment-related morbidity

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 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 protocol summarizes the evidence of three tests and is organized by indication.

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 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 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 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 one 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 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 gene expression profiling with the DecisionDx-Melanoma test to determine whether to perform sentinel lymph node biopsy (SLNB), the evidence includes observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, change in disease status, resource utilization and treatment-related morbidity. The DecisionDx-Melanoma test has two 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 98% in DecisionDx class 1 (low risk) without confidence intervals (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 five 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. There is also not an explicated, evidence-based management pathway for the use of the test. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

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.

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.

BACKGROUND

CUTANEOUS MELANOMA

Cutaneous melanoma accounts for more than 90% of cases of melanoma.[1] 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 9000 people are expected to die of melanoma.[2]

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.[3, 4] There is also a strong association between high total body nevus counts and melanoma.[5]

Several genes appear to contribute to melanoma predisposition such as tumor suppressor gene CDKN2A, melanocortin-1 receptor (MC1R) gene, and BAP1 variants.[6-8] Individuals with either familial or sporadic melanoma have a two to three times increased risk of developing a subsequent primary melanoma.[9] Several occupational exposures and lifestyle factors, such as body mass index and smoking, have been evaluated as possible risk factors for melanoma.[10]

Diagnosis

Primary care providers evaluate suspicious pigmented lesions to determine who should be referred to dermatology. Factors considered include both a patient's risk for melanoma as well as a visual examination of the lesion. The visual examination assesses whether the lesion has features suggestive of melanoma.

Criteria for features suggestive of melanoma have been developed. One checklist is the ABCDE checklist[11]:

- Asymmetry;
- Border irregularities;
- Color variegation;
- Diameter ≥ six mm;
- Evolution.

Another criteria commonly used is the "ugly duckling" sign.[12] An ugly duckling is a nevus that is obviously different from others in a given patient. Primary care providers generally have a low threshold for referral to dermatology.

Melanoma is difficult to diagnose based on visual examination, and the criterion standard for diagnosis is histopathology. There is a low threshold for excisional biopsy of suspicious lesions for histopathologic examination due to the procedure's ease and low risk as well as the high probability of missing melanoma. However, the yield of biopsy is fairly low. The number of biopsies performed to yield one melanoma diagnosis has been estimated to be about 15 for U.S. dermatologists.[13] Therefore a test that could accurately identify those lesions not needing a biopsy (i.e., a rule-out test for biopsy) could be clinically useful.

Treatment and Surveillance

Many treatments and surveillance decisions are determined by a patient's prognostic stage group based the American Joint Committee on Cancer tumor, node, metastasis staging system.[14] The prognostic groups are as follows: stage I, T1a through T2a primary melanomas without evidence of regional or distant metastases; stage II, T2b through T4b primary melanomas without evidence of lymphatic disease or distant metastases; stage III, pathologically documented involvement of regional lymph nodes or in transit or satellite metastases (N1 to N3); stage IV, distant metastases.

Patients may also undergo sentinel lymph node biopsy to gain more definitive information about the status of the regional nodes.

Wide local excision is the definitive surgical treatment of melanoma. Following surgery, patients with American Joint Committee on Cancer stage I or II (node-negative) melanoma do not generally receive adjuvant therapy. Patients with higher risk melanoma receive adjuvant immunotherapy or targeted therapy. Ipilimumab has been shown to prolong recurrence-free survival by approximately 25% compared with placebo at a median of 5.3 years in patients with resected, stage III disease.[15] Nivolumab has been shown to further prolong survival compared with ipilimumab by approximately 35% at 18 months.[16] For patients who are BRAF V600 variant-positive with stage III melanoma, the combination of dabrafenib plus trametinib has been estimated to prolong relapse-free survival by approximately 50% over three years.[17]

Patients with stage I and II disease should undergo an annual routine physical and dermatologic examination. However, follow-up strategies and intervals have not been standardized or tested, and there is no consensus. These patients typically do not receive surveillance imaging. Patients with stage III melanoma may be managed with more frequent follow-up and imaging surveillance following therapy.

Gene Expression Profiling

Gene expression profiling measures the activity of thousands genes simultaneously and creates a snapshot of cellular function. Data for gene expression profiles 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 gene expression profiling include disease diagnosis, disease classification, prediction of drug response, and prognosis.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). The Pigmented Lesion Assay, myPath Melanoma, and DecisionDx-Melanoma tests are available under the auspices of the CLIA. Laboratories that offer LDTs must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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