Protocol

Gene Expression Profiling for Cutaneous Melanoma

(204146)

Medical Benefit		**Effective Date**: 10/01/21	**Next Review Date**: 07/23
Preauthorization	No	**Review Dates**: 07/18, 07/19, 07/20, 07/21, 07/22	

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.

RELATED PROTOCOL

None

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 indeterminate 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 inform management decisions regarding enhanced surveillance	Comparators of interest are: • Sentinel lymph node biopsy • Prognostic tools	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Change in disease status • Resource utilization • 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 inform management decisions regarding adjuvant therapy	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

Populations	Interventions	Comparators	Outcomes
			• Resource utilization • Treatment-related morbidity
Individuals: • With cutaneous melanoma • With clinically negative sentinel node basins who are being considered for sentinel lymph node biopsy	Interventions of interest are: • Gene expression profiling with the DecisionDx-Melanoma test to identify patients who can avoid 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 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.

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. 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. 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 the time to recurrence in node-positive patients. Data on 5-year RFS is not available for the target population (Class 1A patients ≤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.

POLICY

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 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.

MEDICARE ADVANTAGE

For Medicare Advantage the DecisionDx-Melanoma test is **medically necessary** only when the following clinical conditions are met:

1. Patients diagnosed with cutaneous melanoma ≥0.3 mm without distant metastases in Breslow thickness where additional risk stratification information beyond anatomic and pathologic staging will influence management decisions regarding the following:
    - Sentinel Lymph Node Biopsy decision (T1-T2 only)
    - Appropriateness of adjuvant therapy
    - Determining the appropriate level of follow up, imaging, and referrals
2. Patients diagnosed with cutaneous melanoma <0.3 mm in Breslow thickness being considered for sentinel lymph node biopsy:

- in whom there is significant uncertainty about the adequacy of microstaging (positive deep margin), or
- with other adverse features (e.g., very high mitotic index [≥2/mm^2], lymphovascular invasion, or a combination of these factors)

For Medicare Advantage all other DecisionDx-Melanoma testing not meeting the above criteria is **not medically necessary**.

For Medicare Advantage, the myPath Melanoma Assay may be considered **medically necessary** for the diagnosis or exclusion of melanoma from a biopsy when ALL of the following clinical conditions 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.

For Medicare Advantage, the Pigmented Lesion Assay (PLA) may be considered **medically necessary** only for use on:

- Primary melanocytic skin lesions between 5mm and 19 mm
- 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

MEDICARE ADVANTAGE POLICY GUIDELINES

Per current NCCN and ASCO guidelines, SLNB eligible patients are defined as:

- Patients with T1a tumors:
  - in whom there is significant uncertainty about the adequacy of microstaging (positive deep margin), or
  - with Breslow depth <0.8 mm and with other adverse features (e.g., very high mitotic index [≥2/mm^2], lymphovascular invasion, or a combination of these factors)
- Patients with T1b tumors (≥0.8 mm or <0.8 mm with ulceration)
- Patients with T2 tumors

The PLA is indicated for use on melanocytic skin lesions with one or more clinical or historical characteristics suggestive of melanoma, including one or more ABCDE criteria (Asymmetry, Border, Color, Diameter, Evolving) when a clinician trained in the clinical diagnosis of skin cancer is considering the need for biopsy to rule out melanoma.

The purpose of the myPath test is to assist dermatopathologists to arrive at the correct diagnosis of melanoma versus non-melanoma when examining skin biopsies.

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 U.S. 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.[6,7,8] Individuals with either familial or sporadic melanoma have 2 to 3 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]

GENE EXPRESSION PROFILING

Gene expression profiling (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.

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.

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

REFERENCES

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

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70. Wisconsin Physicians Service Insurance Corporation, (Jurisdiction 5 & 8) - California - Entire State, Colorado, Delaware, Hawaii, Maryland, North Carolina, New Mexico, Nevada, Oklahoma, Pennsylvania, Texas, Iowa, Kansas, Kentucky, Missouri - entire state, Nebraska, Illinois, Indiana, Florida, Georgia, Alaska, Arizona, Idaho, Louisiana, Michigan, Montana, North Dakota, Oregon, South Carolina, Utah, Washington, Wyoming, South Dakota, Arkansas, Alabama, Wisconsin, Connecticut, Maine, Massachusetts, Mississippi, New Hampshire, Rhode Island, Vermont, New Jersey, Ohio, Tennessee, Virginia, West Virginia) Local Coverage Determination (LCD): MolDX: Pigmented Lesion Assay (L38178), Original Effective Date for services performed on or after 04/12/2020.
71. Wisconsin Physicians Service Insurance Corporation, (Jurisdiction 5 & 8) - California - Entire State, Colorado, Delaware, Hawaii, Maryland, North Carolina, New Mexico, Nevada, Oklahoma, Pennsylvania, Texas, Iowa, Kansas, Kentucky, Missouri - entire state, Nebraska, Illinois, Indiana, Florida, Georgia, Alaska, Arizona, Idaho, Louisiana, Michigan, Montana, North Dakota, Oregon, South Carolina, Utah, Washington, Wyoming, South Dakota, Arkansas, Alabama, Wisconsin, Connecticut, Maine, Massachusetts, Mississippi, New Hampshire, Rhode Island, Vermont, New Jersey, Ohio, Tennessee, Virginia, West Virginia) Local Coverage Determination (LCD): MolDX: myPath Melanoma ASSAY (L37923), Revision Effective Date For services performed on or after 12/30/2021.
72. Wisconsin Physicians Service Insurance Corporation ,(Jurisdiction 5 & 8) - California - Entire State, Colorado, Delaware, Hawaii, Maryland, North Carolina, New Mexico, Nevada, Oklahoma, Pennsylvania, Texas, Iowa, Kansas, Kentucky, Missouri - entire state, Nebraska, Illinois, Indiana, Florida, Georgia, Alaska, Arizona, Idaho, Louisiana, Michigan, Montana, North Dakota, Oregon, South Carolina, Utah, Washington, Wyoming, South Dakota, Arkansas, Alabama, Wisconsin, Connecticut, Maine, Massachusetts, Mississippi, New Hampshire, Rhode Island, Vermont, New Jersey, Ohio, Tennessee, Virginia, West Virginia) Local Coverage Article: Billing and Coding: MolDX: MELANOMA Risk Stratification Molecular Testing (A56636), Revision Effective Date 07/03/2022.