DRAFT Medical Coverage Policy | Gene Expression Profiling for Cutaneous Melanoma

EFFECTIVE DATE: 04|01|2023
POLICY LAST UPDATED: 12|08|2022

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 (Castle Biosciences)

MEDICAL CRITERIA

Medicare Advantage Plans

DecisionDx Melanoma - 81529

DecisionDx Melanoma may be considered medically necessary when the following criteria are met:

- Patients diagnosed with cutaneous melanoma tumors with clinically negative sentinel node basins who are being considered for SLNB to determine eligibility for adjuvant therapy, and 1 or 2 below:
  1. Cutaneous melanoma ≥ 0.3 mm in Breslow thickness **without distant metastases** where additional information beyond anatomic and pathologic staging:
     - Will influence the decision to perform Sentinel Lymph Node Biopsy (T1-T2 only)
     - Will aid in the determination of appropriate adjuvant therapy
  2. 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/mm2], lymphovascular invasion, or combination of these factors)

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 when the following criteria are met:

- The test is ordered by a board-certified dermatopathologist and;
- The lesion is considered to be a non-metastatic, melanocytic lesion that has not been previously treated, and;
- Testing is an adjunct to histopathology, as a clear distinction between a benign or malignant lesion cannot be made using clinical characteristics and 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, and;
- The results of the gene expression testing will be used in conjunction with the clinical evaluation, histopathological features and other diagnostic procedures to determine and/or alter the treatment plan.

Commercial Products
Not applicable

PRIOR AUTHORIZATION

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

- DecisionDx-Melanoma
- 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:

- DecisionDx-Melanoma
- Pigmented Lesion Assay
- myPath 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.

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."

Pigmented Lesion Assay (PLA)

The Pigmented Lesion Assay test measures expression of 6 genes (PRAME, LINC00518, CMIP, B2M, ACTB, PPIA). The PRAME (PReferentially expressed Antigenin MElanoma) gene encodes an antigen that is preferentially expressed in human melanomas, and that is not expressed in normal tissues (except testis). LINC00518 (Long Intergenic Non-protein Coding RNA518) is a regulatory RNA molecule. The other 4 genes provide normalization values.

The test is performed on skin samples of lesions at least 5 mm in diameter obtained via noninvasive, proprietary adhesive patch biopsies of a stratum corneum specimen. The test does not work on the palms of hands, soles of feet, nails, or mucous membranes, and it should not be used on bleeding or ulcerated lesions.

The Pigmented Lesion Assay test report includes 2 results. The first result is called the PLA MAGE (Melanoma Associated Gene Expression), which indicates low-risk (neither PRAME nor LINC00518 expression was detected),moderate-risk (expression of either PRAME or LINC00518 was detected), or high-risk (expression of both PRAME andLINC00518 was detected). The second result is as an algorithmic Pigmented Lesion Assay score that ranges from 0 to100, with higher scores indicating higher suspicion of malignant disease.

myPath Melanoma
The myPath test measures expression of 23 genes using quantitative reverse-transcription polymerase chain reaction. Fourteen genes are involved in melanoma pathogenesis and are grouped into 3 components related to cell differentiation, cell signaling, and the immune response, and 9 housekeeper genes are also included. The test is performed on 5 standard tissue sections from an existing formalin-fixed, paraffin-embedded biopsy specimen.

The myPath test report includes an algorithmic myPath score ranging from -16.7 to 11.1, with higher, positive scoresindicating higher suspicion of malignant disease. The myPath report also classifies these scores: -16.7 to -2.1 are"benign"; -2.0 to -0.1 are "indeterminate"; and 0.0 to +11.1 are "malignant". The myPath test is meant as an add-on test to standard histopathology.

Commercial Products
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 stage I or II cutaneous melanoma with clinically negative sentinel node basins who are beingconsidered for sentinel lymph node (SLN) biopsy who receive GEP with the DecisionDx-Melanoma test to determinewhether to perform SLN biopsy, the evidence includes retrospective observational studies. Relevant outcomes are overallsurvival, disease-specific survival, test validity, change in disease status, resource utilization, and treatment-relatedmorbidity. The DecisionDx-Melanoma test has 3 independent clinical validity studies that have reported 5-year RFS inAJCC stage I or II patients. Gerami et al (2015) reported RFS rates of 98% in DecisionDx class 1 (low-risk) without CIs, inAJCC stage I or II patients. Zager et al (2017) reported RFS rates of 96% (95% CI, 94% to 99%) for DecisionDx class 1 inpatients with AJCC stage I disease; they also reported RFS rates of 74% (95% CI, 60% to 91%) for DecisionDx class 1 inpatients 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 56patients who were DecisionDx class 1 (low-risk) but SLN biopsy-positive, 22 recurrences (39%) occurred over 5 years. Ifthe DecisionDx test were used as a triage for SLN biopsy, these patients would not undergo SLN biopsy and would likelynot receive adjuvant therapy, which has shown to be effective at prolonging the time to recurrence in node-positivepatients. Data on 5-year RFS is not available for the target population (Class 1A patients ≤55 years old who have tumorsless than 2 mm deep [T1 to T2]) outside of the retrospective cohort that was used to identify the target population. Nodirect evidence of clinical utility was identified. Given that the evidence is insufficient to demonstrate test performance, noinferences can be made about clinical utility through a chain of evidence. The evidence is insufficient to determine that thetechnology results in an improvement in the net health outcome.

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, 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 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 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.

CODING

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 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

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)

RELATED POLICIES

Genetic Testing Services
Proprietary Laboratory Analyses (PLA)

PUBLISHED

Provider Update, February 2023
Provider Update, October 2021
Provider Update, November 2020
Provider Update, April 2019
Provider Update, August 2018

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