Medical Coverage Policy | Gene Expression Profiling for Cutaneous Melanoma

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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:

- Pigmented Lesion Assay (DermTech)
- myPath Melanoma (Myriad)
- DecisionDx-Melanoma (Castle Biosciences)

MEDICAL CRITERIA

BlueCHiP for Medicare

Pigmented Lesion Assay (PLA) – 0089U

The PLA may be considered medically necessary when all of 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) which 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 for the diagnosis or exclusion of melanoma from a biopsy when all of the following criteria 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.

PRIOR AUTHORIZATION

BlueCHiP for Medicare

Prior authorization is required for BlueCHiP for Medicare for the following tests:

- Pigmented Lesion Assay
- myPath Melanoma

BlueCHiP for Medicare and Commercial Products

There is no specific CPT coding for some of the services referenced in this policy. Therefore, an Unlisted CPT code should be used (See Coding Section for details). All Unlisted genetic testing CPT codes require prior authorization to determine what service is being rendered and if the service is covered or not medically necessary. See the Related Policies section.

Prior authorization is required for BlueCHiP for Medicare and recommended for Commercial Products and is obtained via the online tool for participating providers. See the Related Policies section.

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

BlueCHiP for Medicare

The following tests may be considered medically necessary when the medical criteria above are met:

- Pigmented Lesion Assay
- myPath Melanoma

The following test is not covered as the evidence is insufficient to determine the effects of the technology on health outcomes:

- DecisionDx-Melanoma

Commercial Products

The following tests are not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes:

- Pigmented Lesion Assay
- myPath Melanoma
- DecisionDx-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 sunexposed 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.

Pigmented Lesion Assay (PLA)
Pigmented Lesion Assay is a gene expression test using samples collected via adhesive patches provides a non-invasive alternative to the surgical biopsy pathway in the assessment of pigmented skin lesions. The test is positive if LINC00518 and/or PRAME (two genes known to be overexpressed in melanoma) are detected. The PLA is based on a platform technology for non-invasive genomic testing of the skin that allows the analysis of samples collected with an adhesive patch. Four patches are placed on a lesion. For each patch, the margin of the lesion is outlined by the clinician. This outlined tissue is dissected away from the surrounding tissue by the processing laboratory, and RNA is extracted only from the lesional tissue. In contrast to histopathologic sectioning, the adhesive patch method of tissue sampling allows the collection of tissue from the entire the lesion in the plane of the skin surface. Further, genomic information obtained by adhesive patch sampling of the stratum corneum contains information from deeper epidermal cells.

The PLA should not be used on clinically obvious melanoma. It is not intended to be used as a screening test in patients without melanocytic skin lesions. It is also not covered as an adjunctive test in lesions that are considered to already warrant a biopsy. The PLA is a decision tool for atypical melanocytic lesions prior to the decision to biopsy. The PLA result is one element of the overall clinical assessment and should be used in combination with clinical and historical signs of melanoma to obtain additional information prior to a decision to biopsy.

Commercial Products
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 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 the effects of the technology on health outcomes.

myPath Melanoma
The Myriad myPath Melanoma assay is a 23-gene expression signature developed to provide an objective, reproducible, and accurate adjunctive method for differentiating malignant melanoma from benign nevi. The test is intended for use by dermatopathologists confronting primary cutaneous melanocytic neoplasms for which the diagnosis of malignant melanoma versus benign nevus is equivocal / uncertain (i.e. a clear distinction between benign or malignant cannot be achieved using clinical and / or histopathological features alone). Use of the test in these cases increases definitive diagnoses, and evidence suggests it may reduce unnecessary procedures in benign lesions.

The myPath Melanoma test quantifies the expression of 23 genes by quantitative RT-PCR. Fourteen of the 23 genes are known to be over-expressed by malignant melanomas relative to benign nevi. The remaining nine are stably expressed reference genes which allow correction for sample-to-sample variations in RT-PCR efficiency and errors in sample quantification (normalization). The signature genes represent three distinct pathways that contribute to melanoma pathogenesis, including aspects of melanocyte differentiation as well as characteristics of the tumor microenvironment such as cell-cell signaling and tumor-induced host immune responses. The test uses five to seven standard-thickness (4-5 μm) sections taken from the routinely processed formalin-fixed paraffin-embedded (FFPE) tissue of the existing biopsy specimen, allowing its integration into routine clinical practice and its use even in small, early-stage lesions.

The quantified expression of all 23 genes is combined algorithmically and reported as a single numerical score. That number (the myPath Melanoma 'score'), is plotted on a scale that depicts the entire range of scores observed in clinical validation studies. Physicians receive a report showing this single numerical score and the corresponding classification: 'likely malignant', 'likely benign', or 'indeterminate'.

Commercial Products
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 1 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.

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."

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 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 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 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. 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 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 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. Data on five-year RFS is not available for the target population (Class 1A patients ≤55 years old who have tumors less than 2 mm deep [T1-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 the effects of the technology on health outcomes.

CODING

The following CPT codes are covered for BlueCHiP for Medicare when medical criteria above are met and are not medically necessary for Commercial Products:

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 tissue, algorithm reported as a categorical result (ie, benign, indeterminate, malignant)

BlueCHiP for Medicare and Commercial Products
The following Unlisted CPT codes require prior authorization for BlueCHiP for Medicare and Commercial Products. These codes can be used for any test identified in this policy that does not have a specific CPT code.

81479 Unlisted molecular pathology procedure
81599 Unlisted multianalyte assay with algorithmic analysis
84999 Unlisted chemistry procedure

RELATED POLICIES
Genetic Testing Services
Proprietary Laboratory Analyses (PLA)

PUBLISHED
Provider Update, November 2020
Provider Update, April 2019
Provider Update, August 2018

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