Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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(See policy history boxes for previous effective dates)

Title: Gene Expression Profiling for Cutaneous Melanoma

Description/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 2024, about 100,640 new melanomas will be diagnosed (about 59,170 in men and 41,470 in women). About 8,290 people are expected to die of melanoma (about 5,430 men and 2,860 women).[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 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 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 may 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.

Medical Policy Statement

The safety and effectiveness of pigmented lesion assay for the diagnosis of cutaneous melanoma has been established. It may be considered a useful diagnostic option when indicated.

Gene expression profile (GEP) tests that provide a numerical score to assess the likelihood of melanoma are experimental and investigational. The technology has not been demonstrated to improve net health outcomes.

GEP test that classify lesions as having low risk or high risk for metastasis or for locoregional recurrence are experimental and investigational. The technology has not been demonstrated to improve net health outcomes.

Inclusionary and Exclusionary Guidelines

Inclusions:
The use of the **PLA** (DermTech Pigmented Lesion assay) is considered established when **ordered by a dermatologist** to help inform a biopsy decision when **ALL** of the following conditions are met:

- When the lesion size is 5-19 mm;
- When the lesion meets one or more ABCDE criteria (Asymmetry, Border, Color, Diameter, Evolving) ; **or** the individual has pigmented skin making the dermatologist's visual inspection using the ABCDE check list less reliable;
- When the skin is intact (i.e., non-ulcerated or non-bleeding lesions);
- When the lesion is free of psoriasis, eczema, and other similar skin conditions;
- When the lesion does **NOT** contain scar **and:**
    - the location of the lesion is on fragile skin (i.e., dorsum of the hand) **or**
    - is in a location where scarring should be minimized (i.e., on the face) **or**
    - the location is not conducive for biopsy (back of the ear i.e., pinna);
- When the lesion has **NOT** been previously biopsied;
- When the PLA test was **NOT** used for the same lesion before;
- When the lesion is **NOT** already clinically diagnosed as benign or melanoma;

- When the lesion is **NOT** located on the palms of hands, soles of feet, nails, mucous membranes, **or** hair covered areas that cannot be trimmed;
- when the ordering dermatologist has a plan at the time of ordering the test to continue to monitor the skin lesion for changes if the test is negative.
- Only 1 test may be used per patient per clinical encounter, in most cases. In roughly 10% of patients, a second test may be indicated for the same clinical encounter. For rare cases where more than 2 tests are indicated in a single clinical encounter, an appeal with supporting documentation may be submitted for additional tests.

Exclusions:
- Pigmented Lesion Assay testing when the above criteria is not met.
- myPath Melanoma testing
- DecisionDx-Melanoma testing
- All other Gene Expression Profile testing for cutaneous melanoma

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CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

0089U

Other codes (investigational, not medically necessary, etc.):

81479 81529 81599 84999

0314U

Note: Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

GENE EXPRESSION PROFILING TO GUIDE INITIAL BIOPSY DECISIONS

Clinical Context and Test Purpose

The purpose of gene expression profiling (GEP) in individuals who have suspicious pigmented lesions being considered for biopsy is to inform a decision about whether to biopsy.

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

- **A**symmetry;
- **B**order irregularities;
- **C**olor variegation;
- **D**iameter ≥6 mm;
- **E**volution.

Another criterion 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.

The purpose of GEP in patients who have suspicious pigmented lesions being considered for biopsy is to inform a decision about whether to biopsy.

The following **PICO** was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with suspicious pigmented lesions being considered for referral for biopsy, specifically those lesions meeting one or more ABCDE criteria.

Interventions

The test being considered is the DermTech Pigmented Lesion Assay (PLA). The PLA test measures expression of 6 genes (*PRAME*, *LINC00518*, *CMIP*, *B2M*, *ACTB*, *PPIA*). The *PRAME* (PReferentially expressed Antigen in MElanoma) gene encodes an antigen that is preferentially expressed in human melanomas, and that is not expressed in normal tissues (except testis).[14] LINC00518 (Long Intergenic Non-protein Coding RNA518) is a regulatory RNA molecule. The other 4 genes provide normalization values.[15] The feasibility of a test like PLA was first described in Wachsman et al (2011) and Gerami et al (2014)[16,17] and development of the specific PLA test was described in Gerami et al (2017).[18]

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.[15]

The PLA 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* and *LINC00518* was detected). The second result is as an algorithmic PLA score that ranges from 0 to 100, with higher scores indicating higher suspicion of malignant disease.[15]

The PLA sample report states that for low-risk lesions, physicians should "consider surveillance," while for moderate- and high-risk lesions, physicians should "recommend a biopsy." It does not state whether lesions with negative results should be further evaluated with dermoscopy or other techniques to confirm the lesion should not be biopsied. Therefore, this evidence review evaluates the test as a replacement for dermoscopy. As mentioned previously, there is a low threshold for biopsy of suspicious lesions. As such, tests that can rule-out need for biopsy could be useful and thus sensitivity and negative predictive value are the performance characteristics of most interest.

Comparators
After a referral from primary care to dermatology settings, dermatologists use visual examination as well as tools such as dermoscopy to make decisions regarding biopsy of suspicious lesions. A meta-analysis of 9 studies (8487 lesions with 375 melanomas) compared dermoscopy with visual examination alone for the diagnosis of melanoma; it reported that, for clinicians with training in dermoscopy, adding dermoscopy to visual examination increased the sensitivity from 71% to 90%. The specificity numerically increased from 80% to 90%, but the difference was not statistically significant.[19] Although dermoscopy is noninvasive and may aid in decision making regarding biopsy, it is only used by approximately 50% to 80% of dermatologists in the United States due to lack of training, interest, or time required for the examination.[20,21]

The reference standard for diagnosis of melanoma is histopathology.

Outcomes
The beneficial outcomes of a true positive test result are appropriate biopsy and diagnosis of melanoma. The beneficial outcome of a true negative test result is potentially avoiding unnecessary biopsy.

The harmful outcome of a false-positive result is having an unnecessary biopsy. The harmful outcome of a false-negative result is potential delay in diagnosis and treatment.

The timeframe of interest for calculating performance characteristics is time to biopsy result. Patients who forgo biopsy based on test results could miss or delay diagnosis of cancer. Longer follow-up would be necessary to determine the effects on overall survival.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Determining whether a test can guide biopsy decisions is not based only on its sensitivity and specificity, but also on how the accuracy of the existing pathway for making biopsy decisions is changed by the test. Therefore, the appropriate design for evaluating performance

characteristics depends on the role of the new test in the pathway for making biopsy decisions. New tests may be used as replacements for existing tests, to triage who proceeds for existing tests or add-on tests after existing tests. For replacement tests, the diagnostic accuracy of both tests should be concurrently compared, preferably in a paired design (i.e., patients receive both tests), and all patients receive the reference standard. For a triage test, a paired design is also needed, with the reference standard being performed preferably on all patients but at least for all discordant results. For an add-on test, the included patients can be limited to those who were negative after existing tests with verification of the reference standard in patients who are positive on the new test.[22]

Study Selection Criteria

For the evaluation of clinical validity of the PLA test, studies that meet the following eligibility criteria were considered:

- Reported on a validation cohort that was independent of the development cohort;
- Reported on the accuracy of the marketed version of the technology;
- Included a suitable reference standard (histopathology);
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Review of Evidence

Studies were excluded from the evaluation of the clinical validity of the PLA test because they reported results of the development cohort,[17] they did not use the marketed version of the test,[16,17] did not adequately describe the patient characteristics,[23] or did not adequately describe patient selection criteria.[24]

Gerami et al (2017) sought to provide clinicians with a noninvasive diagnostic tool for the histopathologic assessment of pigmented skin lesions. A 2-gene classification method based on LINC00518 and preferentially expressed antigen in melanoma (PRAME) gene expression was evaluated and validated in 555 pigmented lesions (157 training and 398 validation samples) obtained noninvasively via adhesive patch biopsy. Results were compared with standard histopathologic assessment in lesions with a consensus diagnosis among 3 experienced dermatopathologists. In 398 validation samples (87 melanomas and 311 nonmelanomas), LINC00518 and/or PRAME detection appropriately differentiated melanoma from nonmelanoma samples with a sensitivity of 91% and a specificity of 69%. The authors established LINC00518 and PRAME in both adhesive patch melanoma samples and underlying formalin fixed paraffin embedded (FFPE) samples of surgically excised primary melanomas and in melanoma lymph node metastases. This noninvasive 2-gene pigmented lesion assay classifies pigmented lesions into melanoma and nonmelanoma groups and may serve as a tool to help with diagnostic challenges that may be inherently linked to the visual image and pattern recognition approach.[18]

Table 1. Clinical Validity Study Characteristics of the PLA Test for Diagnosing Melanoma

Study	Study Population	Design	Reference Standard for Dx of Melanoma	Threshold Score for PLA Test	Timing of Reference and PLA Tests	Blinding of Assessors
Gerami et al (2017)[18]	• Adults • Suspicious pigmented lesion ≥ 4mm in diameter • W/O obvious or suspicious nodular melanoma • 24% from extremities, 13% from head and neck, 62% from trunk • 55% of samples from men • Median age, 49 y (range, 19-97 y)	Retrospective, Not consecutive or random	Histopathology; consensus diagnosis	• Quantitative PCR yielded an amplification curve and a measurable cycle threshold value • Either *LINC00518* or *PRAME* detected	PLA patch before surgical biopsy; timing between patch and surgical biopsy unclear	Not clear

W/O: without; Dx: diagnosis; PCR: polymerase chain reaction

Table 2. Clinical Validity Study Results of the PLA Test for Diagnosing Melanoma

Study	Initial N	Final N	Excluded Samples	Melanoma Prevalence	Sensitivity[b]	Specificity[b]	PPV[b]	NPV[b]
Gerami et al (2017)[18]	398[a]	398	Before allocation to Training and validation cohorts, 11% of original samples excluded due to lack of consensus diagnosis	22%	91 (83 to 96)	69 (64 to 74)	45 (38 to 53)[c]	96 (93 to 98)[c]

NPV: negative predictive value; PPV: positive predictive value.
[a] 398 samples were included in the validation cohort; the number of independent patients is unclear.
[b] Values are percentages with 95% confidence interval.
[c] Confidence intervals provided in the report; calculated from data provided.

Table 3. Clinical Validity Study Relevance Gaps of the PLA Test

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Gerami et al (2017)[18]	3. Study population characteristics not adequately described		3. No comparison to dermoscopy	3. Predictive values were not reported but were calculated	

				based on data provided	

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 4. Clinical Validity Study Design and Conduct Gaps of the PLA Test

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Completeness of Follow-Up[e]	Statistical[f]
Gerami et al (2017)[18]	1,2. Not clear what criteria used to select samples but it does not appear to have been random or consecutive	1. Blinding of histopathology readers not described	1.Patch biopsy administered before surgical biopsy but timing between procedures not described	1. No registration reported		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Follow-Up key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Clinically Useful

A test is clinically useful if the results inform management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No direct evidence of clinical utility was identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility through a chain of evidence.

A decision-impact study by Ferris et al (2017) assessed the potential impact of PLA on physicians' biopsy decisions in patients.[24] Forty-five dermatologists evaluated 60 clinical and dermoscopic images of atypical pigmented lesions (8 melanoma, 52 nonmelanoma). In the first

round, dermatologists did not have PLA test results and, in the second round, dermatologists had access to PLA test results with the order of cases being scrambled. The dermatologists were asked whether the lesions should be biopsied after each round. Forty-five dermatologists (29 male and 16 female) performed the evaluation.
After incorporating the PLA into their decision as to whether to biopsy a pigmented lesion suggestive of melanoma, dermatologists improved their mean biopsy sensitivity from 95.0% to 98.6% (P = .01); specificity increased from 32.1% to 56.9% (P < .001) with PLA data. The noninvasive PLA enables dermatologists to improve biopsy specificity while maintaining or improving sensitivity. This result may increase the number of early melanomas biopsied and reduce the number of benign lesions biopsied, thereby improving patient outcomes and reducing health care costs.[24]

According to Skelsey et al (2021), management of pigmented lesions currently relies on visual assessment with surgical biopsy and histopathologic examination for those lesions suspicious for melanoma.[70] A non-invasive genomic assay that detects two melanoma-associated biomarkers (PLA, 2-GEP) has recently been validated as an adjunct to visual assessment for distinguishing high-risk pigmented lesions appropriate for biopsy from those that can be safely monitored via clinical surveillance. Ten early-stage melanomas (4 *in situ* and 6 pT1a) were identified among 1,233 PLA-negative lesions (0.8%), corresponding to a real-world NPV of 99.2% (CI 95% = 98.5 - 99.6). Of 302 initially PLA-negative lesions subjected to repeat testing an average of 15 months later, 34 were PLA-positive. Biopsy revealed 3 melanomas (all *in situ*), further confirming an NPV of > 99%. Among 316 PLA-positive cases, 59 were diagnosed as melanoma by histopathology, corresponding to a PPV of 18.7%. Of all PLA-positive lesions, 30.5% had histopathologic diagnoses corresponding to high-risk MPATH-Dx categories (Classes III-V). The PLA has an NPV of >99% within the real-world intended use population. The PLA has a PPV of 18.7% for melanoma and also detects high-risk lesions such as dysplastic nevi with severe / high-grade atypia that are generally targeted for complete excision.

Siegel et al (2022) evaluated the potential savings to health plans when the PLA is incorporated into the assessment of pigmented lesions clinical suspicious for melanoma.[71]
A Return on Investment (ROI) model was developed from a US payor perspective to determine the per member per month (PMPM) net savings impact of incorporating PLA into the visual assessment/histopathology (VAH) pathway. Using 2019 claims data for patients with lesions suspicious for melanoma (N=239,854), use of PLA in year 1 was modeled and followed through subsequent years. Costs were assessed through the pathway of initial visual assessment, surgical procedure(s), histopathology, and subsequent management.
The ROI model predicted annual net savings of $0.54 PMPM for commercial health plans over a three-year period with incorporation of PLA into the VAH pathway. In this analysis, 95.7% of surgically assessed lesions clinically suspicious for melanoma were diagnosed as benign, with 30.4% of patients with benign lesions undergoing a more advanced procedure (e.g., excision), either initially or following a biopsy. Melanoma diagnosis rates associated with biopsy only, excision only, and biopsy followed by excision procedures in the VAH pathway were 0.9%, 0.1%, and 17.9%, respectively. Incorporation of the PLA into the VAH pathway for assessing suspicious pigmented lesions results in savings for commercial health insurance plans. Use of the PLA improves patient care by using genomic assessments to minimize avoidable surgical procedures on benign lesions, enrich the population of melanomas diagnosed, and decrease downstream costs of late-stage melanoma diagnoses.

Section Summary: Gene Expression Profiling to Guide Initial Biopsy Decisions

The diagnostic yield of early stage melanoma on biopsied tissue is limited. Histopathologic assessment of early stage biopsied melanoma tissue is challenging and has significant discordance between pathologists. While fellowship-trained board certified dermatopathologists tend to have a higher accuracy than other pathologists, under-interpretation is likely. Conventional melanoma care may lead to both biopsies of non-malignant lesions, and even in those patients who do have a biopsy the diagnosis of a malignancy may be missed. As such, there is potential clinical utility for a test that can either spare a patient the need for a biopsy. The Pigmented Lesion Assay (PLA) was developed to fill the niche of reducing the biopsy rate of non-malignant lesions.

GEP FOR DIAGNOSING LESIONS WITH INDETERMINATE HISTOPATHOLOGY

Clinical Context and Test Purpose

The diagnosis of melanoma was described in the previous section. The diagnosis of melanoma is histopathologic and when the histopathologic diagnosis is straightforward, ancillary methods such as comparative genomic hybridization, florescence in situ hybridization (FISH), and GEP are not recommended. Therefore the usefulness of an ancillary test is its ability to predict biologic behavior (metastasis) of lesions that are indeterminate by histopathology.

The purpose of GEP in patients whose melanocytic lesion is indeterminate after histopathology is to aid in the diagnosis of melanoma and decisions regarding treatment and surveillance.

The following **PICO** was used to select literature to inform this review.

Populations

The relevant population of interest is individuals whose melanocytic lesion is indeterminate based on clinical and histopathologic features.

Interventions

The test being considered is the Myriad myPath Melanoma test. 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 scores indicating higher suspicion of malignant disease.[25] 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”. Development of the test has been described by Clarke et al (2015).[26]

The myPath test is meant as an add-on test to standard histopathology. Studies have evaluated the performance characteristics of the test when histopathology is used as the reference standard,[26,27,28] but are not the focus of this evidence review given that the test's potential usefulness is in evaluation of indeterminate lesions.

No recommendations for treatment or surveillance are given on the report.

Comparators

The reference standard for diagnosis of melanoma is histopathology. However, in cases of indeterminate histopathology, long-term follow-up is needed to evaluate the clinical outcome, specifically metastasis.

Comparative genomic hybridization and FISH are also used to diagnosis indeterminate lesions although neither has been fully validated. FISH has been evaluated as a tool to aid in the diagnosis of lesions that are indeterminate, following histopathology in two studies that included histologically ambiguous lesions and a clinical, long-term follow-up. One study reported by Gaiser et al (2010) included 22 melanocytic lesions (12 indeterminate) followed for a mean of 65 months (range, 10-156 months) and reported a FISH sensitivity of 60% and a specificity of 50% for development of metastases during follow-up.[29] A second study, reported by Vergier et al (2011), included 90 indeterminate melanocytic lesions of which 69 had no recurrence for at least 5 years of follow-up (mean, 9 years; range, 5-19 years) and 21 lesions that exhibited metastases. The sensitivity and specificity rates of the histopathologic review combined with FISH for the clinical outcome were 76% and 90%, respectively.[30]

Outcomes
The beneficial outcomes of a true positive test result are a diagnosis of melanoma and corresponding appropriate treatment and surveillance. The beneficial outcome of a true negative test result is avoiding unnecessary surgery.

The harmful outcome of a false-positive result is having an unnecessary surgery and surveillance. The harmful outcome of a false-negative result is a delay in diagnosis and treatment.

The National Comprehensive Cancer Network guidelines state that even in the presence of node metastasis, indeterminate neoplasms can demonstrate benign biologic behavior, making it difficult to define a fully malignant lesion and also states that events in the group of indeterminate lesions tend to occur late. Therefore, the guidelines suggest that long-term follow-up is necessary to validate a test for this purpose.

Recurrence and metastases can occur may years after treatment of melanoma. In the two studies evaluating long-term outcomes of FISH (described above), the mean follow-up was approximately 5.5 and nine years.[29,30] In Vergier et al (2011), metastases in the FISH-negative group generally occurred by 5 years.[30]

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Study Selection Criteria
For the evaluation of clinical validity of the myPath test, studies that meet the following eligibility criteria were considered:

- Reported on a validation cohort that was independent of the development cohort;
- Reported on the accuracy of the marketed version of the technology;
- Included a suitable reference standard (final clinical diagnosis with at least 5 years of follow-up for negatives);
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Review of Evidence

Observational Studies

Studies were excluded from the evaluation of the clinical validity of the myPath test because authors did not use an appropriate reference standard,[26-28,31-33] or did not adequately describe patient characteristics.[26]

Two studies met inclusion criteria. Study characteristics are described in Table 5, and results in Table 6. Study relevance, design, and conduct limitations are in Tables 7 and 8.

The Ko et al (2017) clinical validity study met selection criteria.[34] The study characteristics are described in Table 5. In Ko et al (2017), archived melanocytic neoplasms were submitted for myPath testing from university clinics in the United States and United Kingdom with additional samples acquired from Avaden BioSciences.[33] Stage I, II, and III primary cutaneous melanomas that produced distant metastases subsequent to the diagnosis and benign lesions with clinical follow-up and no evidence of recurrence of metastases were included. For benign samples, a disease-free time of at least 5 years was recommended. Information on the previous testing was not provided. It is not clear if any of the samples originally had indeterminate histopathology results. Dates of data collection were not reported. Sex, age, Breslow depth, and anatomic location were described; presenting symptoms were not reported. A total of 293 samples were submitted; of these 53 did not meet inclusion criteria and 58 (24% of those tested) failed to produce a valid test score. An additional seven samples with indeterminate results were excluded from the calculations of performance characteristics.

In a retrospective study using archived samples from a previous validation study, Clarke et al (2020) evaluated the performance of myPath in a population of diagnostically uncertain melanocytic neoplasms as compared with clinical outcomes.[35.] Diagnostic uncertainty was defined as at least 1 dermatopathologist: selecting indeterminate as the diagnosis; selecting a diagnosis that was discordant with other dermatopathologists; indicating a need for additional diagnostic workup, or indicating a preference for peer consultation before rendering a final diagnosis. Participating institutions were encouraged to submit lesions with at least 5 years of metastasis-free follow-up, but the length of follow-up was not an inclusion criterion. The median follow-up time for benign lesions was 74.9 months (interquartile range [IQR]: 57.9 to 114.7) and 69% (57/83) of cases had a follow-up of at least 5 years. The median time to metastasis for the malignant cases was 17 months (IQR:10.3 to 37.6).

Table 5. Clinical Validity Study Characteristics of the myPath Test for Diagnosing Melanoma

Study	Study Population	Design	Reference Standard for Diagnosis of Melanoma	Threshold Score for Positive myPath Test	Timing of Reference and myPath Tests	Blinding of Assessors
Ko et al (2017)	• Primary cutaneous melanomas or benign melanocytic nevi • Mean age, 53 y • 55% of samples from men	Retrospective not consecutive or randomly selected	• For positive melanoma diagnosis: malignant lesions that produced distant metastases • For negative melanoma diagnosis: event-free follow-up, recommender 5 y (median, 6.2 y)	Scores from 0.0 to 11.1 (i.e., "malignant")	• Final clinical diagnosis established before myPath test • Length of time between biopsy and myPath test unclear	yes
Clarke et al (2020)	Melanocytic neoplasms with diagnostic uncertainty Mean age 63.4 years, 32.7% female (malignant lesions), 42.4 years, 65.1% female (benign lesions)	Retrospective; archived lesions obtained as part of a previous validation study. Case eligibility determined by clinical outcome; otherwise unselected	Positive: malignant outcome defined as the detection of distant metastasis subsequent to initial biopsy. Lesions known to be malignant at initial biopsy excluded; otherwise no minimum follow-up interval. Negative: benign outcome was defined as absence of local recurrence or metastases throughout a protracted clinical follow-up period (5-year follow-up was not required).	Scores from 0.0 to 11.1 (i.e., "likely malignant")	Retrospective testing using archived samples.	Yes

Table 6. Clinical Validity Study Results of the myPath Test for Predicting Metastasis

Study	Initial N	Final N	Excluded Samples	Melanoma Prevalence	Sensitivity[a]	Specificity[a]	PPV[a]	NPV[a]
Ko et al (2017)	240	175	• 58 failed to produce test results • 7 with intermediate results	54	94 (87 to 98)[b]	96 (89 to 99)[b]	97 (91 to 99)[b]	93 (85 to 97)[b]
Clarke et al (2020)	182	125	56 not considered to be diagnostically	44.1%	90.4 (79 to 96.8)	95.5 (87 to 99.1)	94.0 (83.8 to 97.9)	92.7 (84.6% to 96.7)

			uncertain; 1 missing slide					

NPV: negative predictive value; PPV: positive predictive value.
[a] Values are percentages with 95% confidence interval.
[b] Confidence intervals not provided in the report; calculated from data provided.

Table 7. Clinical Validity Study Relevance Gaps of the myPath Test

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Ko et al (2017)	4. Study population is not limited to lesions that are indeterminate following histopathology		3. No comparison to CGH or FISH		None noted
Clarke et al (2020)					1. Participating institutions were encouraged to submit lesions with at least 5 years of metastasis-free follow-up, but length of follow-up was not an inclusion criterion. 69% (57/83) of cases had 5-year follow-up

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. CGH: comparative genomic hybridization; FISH: fluorescence in situ hybridization.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 8. Clinical Validity Study Design and Conduct Gaps of the myPath Test

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Completeness of Follow-Up[e]	Statistical[f]
Ko et al (2017)	2. Samples not consecutive or random		1. Unclear how much time elapsed between biopsy	1. No registration reported	2. More than 25% of samples tested did not produce	1. CIs for sensitivity and specificity not reported but were calculated based on

			and myPath test		results or produced indeterminate results	data provided. NPV, PPV were not reported
Clarke et al (2020)	2. Selection not random or consecutive; multiple exclusions			1. No registration reported	Unclear how many samples excluded prior to 182 identified as eligible	

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Follow-Up key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Clinically Useful

A test is clinically useful if the results inform management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No direct evidence of clinical utility was identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Two decision-impact studies assessed the potential impact of myPath on physicians' treatment decisions in patients with diagnostically challenging lesions. [36,37] Given the lack of established clinical validity and no reported long-term outcomes, it is not known whether any treatment changes were clinically appropriate.

Section Summary: Gene Expression Profiling for Diagnosing Lesions with Indeterminate Histopathology

Multiple high-quality studies are needed to establish the clinical validity of a test. The myPath test has 21 clinical validity study 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. There is no direct evidence of clinical utility. A chain of evidence for clinical utility cannot be constructed due to the lack of robust evidence of clinical validity.

GEP TO GUIDE MANAGEMENT DECISIONS IN MELANOMA

Clinical Context and Test Purpose

Many treatments and surveillance decisions are determined by an individual's prognostic stage group based the American Joint Committee on Cancer tumor, node, metastasis staging system.[38] 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.[39] Nivolumab has been shown to further prolong survival compared with ipilimumab by approximately 35% at 18 months.[40] 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 3 years.[41]

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.

The purpose of GEP in patients with melanoma is to identify low and high-risk patients classified as stage I or II according to the AJCC) criteria. Current guidelines do not recommend adjuvant therapy or imaging surveillance for AJCC stage I or II patients following surgery. Patients initially staged as I or II who have positive lymph nodes following sentinel lymph node biopsy (SLNB) are then eligible to be treated with adjuvant therapy as stage III patients.

At least three uses for the test have been suggested. The manufacturer's website has suggested that physicians can use DecisionDx-Melanoma information to "consider upstaging" patients for "active systemic surveillance or referral to medical oncology for consideration of systemic drug therapy or clinical trials." Similarly, in one clinical validity study (described below), the authors stated that "high-risk patients with stage I and II disease may benefit from adjuvant therapy and/or enhanced imaging protocols to allow for early detection of metastasis."[42] In another clinical validity study, the authors concluded that the test's "role in consideration of patients for adjuvant therapy should be examined prospectively."[43] This use of the test would be as a replacement for SLNB since SLNB is currently used to identify patients clinically diagnosed as stage I and II who have node involvement.

The manufacturer's website has suggested that physicians can use DecisionDx-Melanoma information to guide decisions regarding:

1. "Whether to perform a sentinel lymph node biopsy surgical procedure for eligible patients 55 years of age and older who have tumors less than 2 mm deep (T1-T2)"
2. "Deciding what level of follow-up, imaging, and referrals are appropriate for any patient with a tumor at least 0.3 mm deep."

The use of the test reviewed for the Medicare population is to select patients at low-risk of being lymph node-positive who can avoid an SLNB (i.e., a triage test for SLNB).

The following **PICO** was used to select literature to inform this review.

Populations
To select individuals for adjuvant therapy and/or enhanced surveillance, the relevant population of interest are patients with AJCC stage I/II cutaneous melanoma.

To select individuals who can avoid SLNB, the relevant population of interest are patients with AJCC stage I or II cutaneous melanoma who are being considered for SLNB.

Interventions
The test being considered is the Castle Biosciences DecisionDx-Melanoma test. 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.

Development of the test was described in Gerami et al (2015).[42] To develop the DecisionDx-Melanoma gene panel, Gerami et al (2015) conducted a meta-analysis of published studies that identified differential gene expression in metastatic vs. nonmetastatic primary cutaneous melanoma. Of 54 identified genes, investigators selected 20 for further polymerase chain reaction analysis based on chromosomal location. Five genes from Castle Biosciences' DecisionDx-UM gene panel were added based on analysis of metastatic and nonmetastatic primary cutaneous melanoma, and 2 probes of the *BRCA1*-associated protein 1 gene, *BAP1*, which has been associated with the metastatic potential of uveal melanoma, also were added. Finally, 4 genes with minimal variation in expression level between metastatic and nonmetastatic primary cutaneous melanoma were added as controls. Patients had a minimum follow-up of 5 years unless there was a well-documented metastatic event, including positive SLNB. Information about treatments received was not provided.

The DecisionDx test report provides 2 results: a class and a probability score. The class stratifies tumors as low risk (class 1) or high risk (class 2), with subclassifications within each class (A or B) based on how close the probability score is to the threshold between class 1 and class 2. The probability score ranges from 0 to 1 and appears to be the risk of recurrence within 5 years.

DecisionDx is meant to be used as a triage test with respect to SLNB. However, the sample report makes no recommendations for SLNB, treatment, or surveillance based on test results.

Comparators
Treatment and surveillance recommendations are based on AJCC staging. SLNB may be used to get more definitive information about the status of the regional nodes compared with a physical examination. The American Society of Clinical Oncology[40] and National Comprehensive Cancer Network have similar but not identical recommendations on which patients should undergo SLNB (patients with thickness more than approximately 1 mm or thin melanomas with other high-risk features). SLNB has a low rate of complications; in the Sunbelt Melanoma Trial, a prospective multi-institutional study of SLNB for melanoma reported by

Wrightson et al (2003), less than 5% of the 2120 patients developed *major* or *minor* complications associated with SLNB.[44]

Online tools are available to predict prognosis based on the AJCC guidelines. The original AJCC tool was developed by Soong et al (n.d.).[45] Callender et al (2012) incorporated SLNB results into a revised tool (http://www.melanomacalculator.com/).[446]

Outcomes

Regarding selecting patients for adjuvant therapy and/or enhanced surveillance in AJCC stage I or IIA patients:

A negative DecisionDx (class 1) test result would not change outcomes. Per guidelines, the patients would not receive adjuvant therapy or enhanced surveillance, just as without the DecisionDx test. A positive DecisionDx (class 2) test result would indicate that a patient might benefit from adjuvant therapy or enhanced surveillance. Therefore, the potential beneficial outcomes of a true positive result are additional treatment and surveillance and potentially prolonged survival. The potential harmful outcomes of a false-positive result are unnecessary adverse effects and burdens of adjuvant therapy and enhanced surveillance.

Regarding selecting patients who can avoid SLNB:

For patients meeting guideline-recommended criteria for SLNB, a positive DecisionDx (class 2) test result would not change outcomes. The patients would proceed to SLNB, as they would have without the DecisionDx test, and treatment and imaging decisions would depend on SLNB results. A negative DecisionDx (class 1) test result would indicate that a patient could avoid an SLNB. Therefore, the potential beneficial outcomes of a negative result are avoidance of an SLNB. The potential harmful outcomes of a negative result are reduced time to recurrence due to not identifying node-positive patients that would be eligible for beneficial adjuvant treatment.

The risk of recurrence decreases over time but does not reach zero. In a study of 1568 patients with stage I melanoma, Dicker et al (1999) found that 80% of the recurrences occurred within the first 3 years.[46] A prospective study by Garbe et al (2003) reported that, for stage I and II patients, the risk of recurrence was low after 4.4 years.[47] Among 4731 patients treated for more than 10 years at 1 institution, Faries et al (2013) found the majority of recurrences occurred in the first 5 years.[48] However, 7% of patients experienced recurrence after 10 years (median, 16 years). Even among stage I/II patients, recurrence after 10 years occurred in 2% of patients.

Clinically Valid

Study Selection Criteria

For the evaluation of clinical validity of the DecisionDx test, studies that meet the following eligibility criteria were considered:

- Reported on a validation cohort that was independent of the development cohort;
- Reported on the accuracy of the marketed version of the technology;
- Included a suitable reference standard (5-year RFS);
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Review of Evidence

Several papers were excluded from the evaluation of clinical validity. Hsueh et al (2017), Podlipnik et al (2019), and Hsueh et al (2021) was excluded from the evaluation of the clinical validity of the DecisionDx test because it did not report 5-year outcomes (median follow-up, 1.5 years, 2 years and 3.2 years). [50,51,52] Samples used in Gerami et al (2015)[42] and Ferris et al (2017)[24] appear to overlap with the samples from Gerami et al (2015)[41] and each other and will not be considered independent validation studies for inclusion in the tables. They are described briefly following the clinical validity tables. Samples used in both papers by Gastman et al (2018) are stated to overlap previous validation studies.[53,54,42,43] Vetto et al (2019) included a retrospective cohort that was used to develop the model and is thus not eligible for inclusion, as well a prospective cohort with some overlapping samples and without report of 5-year outcomes.[55] Marks et al (2019) describes the development of a cutpoint.[56.]

Four independent clinical validity studies meeting eligibility criteria have been conducted. Characteristics and results are summarized in Tables 9 and 10 and briefly in the paragraphs that follow.

Table 9. Clinical Validity Study Characteristics of the DecisionDx Test for Diagnosing Melanoma

Study	Study Population	Design	Reference Standard/ Outcome Measure	Threshold Score for Positive DecisionDx Test	Timing of Reference and Decision Dx Tests	Blinding of Assessors
Gerami et al (2015); Validation subset	• Adults • Stage 1-IV cutaneous melanoma (87%) stage I/II) • At least 5 y of FU (median, 7.0 y)	Retrospective, not consecutive or randomly selected	5-y RFS	• Class 2 is high risk • Risk threshold not provided	• Patient diagnosed between 1998 and 2009 • Timing of DecisionDx not described	Yes
Zager et al (2018)	• Stage I-III cutaneous melanoma (68% stage I/II) • At least 5 y of FU (median, 7.5 Y)	Retrospective, not consecutive or randomly selected	5-y RFS	• Class 2 is high risk • Class 1: probability score 0 to 0.49 • Class 2: probability score 0.5 to 1	• Patients diagnosed between 2000 and 2014 • Timing of DecisionDx not described	Yes

Greenhaw et al (2018)	Patients who were treated for primary invasive CM of any Breslow depth within the last 5 years and had GEP testing (86% stage I, 14% stage II) Mean follow-up of 23 months; only 20 patients had 5-year follow-up	Retrospective Consecutive	5-y MFS	Commercial test cutoffs used	Institution offered DecisionDx testing to newly diagnosed and those treated within the previous five years	Yes
Keller et al (2019)	Patients had CM (91% stage I/II), opted for GEP testing and underwent SNB and wide excision of primary tumor. Median follow-up time, 3.5 years Median Breslow thickness, 1.4 mm 9% SLN positive	Prospective	3-yr RFS	Commercial test cutoffs used	Patients diagnosed between 2013 and 2015 GEP reported to be performed concurrently with SNB	Yes

DFS: disease-free survival; FU: follow-up; RFS: recurrence-free survival; MFS:metastasis-free survival; GEP: gene expression profiling

Table 10. Clinical Validity Study Results of the DecisionDx Test for Diagnosing Melanoma

Study	Initial /Final N	Excluded Samples	Events and Kaplan-Meier 5-Year RFS[a]		Sensitivity[a]	Specificity[a]	PPV[a]	NPV[a]
			Class 1	Class 2				
Gerami et al (2015); Validation Subset		Samples excluded if melanoma dx not confirmed, dissectible area not acceptable						
Overall	Unclear /104		• 4 events • RFS=97 (NR)	• 31 events • RFS=31 (NR)	89 (73 to 97)[b]	83 (72 to 91)[b]	72 (56 to 85)[b]	93 (84 to 98)[b]

				• P<0.001 vs. class I				
AJCC stage I and II	Unclear /78		• 3 events • RFS=98 (NR)	• 18 events • RFS=37 (NR) • P<0.001 vs. class I	86 (64 to 97)[b]	84 (72 to 93)[b]	67 (46 to 83)[b]	94 (84 to 99)[b]
Zager et al (2018)		Did not meet analytic quality control threshold						
Overall	601/523		• 42 events • RFS=88 (85 to 92)	• 100 events • RFS=52 (46 to 60)	70 (62 to 78)	71 (67 to 76)	48 (41 to 55)	87 (82 to 90)
AJCC stage I	Unclear /264		• 11 events • RFS=96 (94 to 99)	• 6 events • RFS=85 (74 to 97)	35 (14 to 62)[b]	87 (82 to 91)[b]	15 (6 to 31)[b]	95 (91 to 98)[b]
AJCC Stage II	Unclear /93		• 9 events • RFS=74 (60 to 91)	• 30 events • RFS=55 (44 to 69)	77 (61 to 89)[b]	43 (29 to 57)[b]	49 (36 to 62)[b]	72 (53 to 86)[b]
Greenhaw et al (2018)	256/256	None excluded but only 20 had 5-y follow-up	3 events MFS=93 (82-100)	8 events MFS=69 (52-90)	77 (46-94)	87 (82-91)	24 (13-40)	99 (96-100)
Keller et al (2019)[56]	159/174	15 patients had insufficient tumor for GEP testing	events unclear at year 5 RFSc ~ 97 (NR)	events unclear at year 5 RFSc ~ 40 (NR)	NR	NR	NR	NR

AJCC: American Joint Committee on Cancer; CI: confidence interval; Dx: diagnosis; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; RFS: recurrence-free survival.
[a] Values are percentages with 95% confidence interval.
[b] Confidence intervals not provided in the report; calculated from data provided.

The validation cohort in Gerami et al (2015) included patients with stage 0, I, II, III, or IV disease from 6 U.S. centers (N=104).[42] A complete disposition of samples received from the institutions and those included in the analysis was not provided. For 78 patients in the validation cohort with AJCC stage I or II cutaneous melanoma who had either a metastatic event or had more than 5 years of follow-up without metastasis, 5-year disease-free survival was 98% (CIs not reported) for DecisionDx class I patients and 37% for DecisionDx class II patients. The positive predictive value (PPV) and negative predictive value (NPV) were 67% and 94%, respectively. CIs for performance characteristics were calculated in Table 10 based on data provided. Reclassification of patients in AJCC stages to DecisionDx classes is shown in Table 11.

Table 11. Reclassification of Patients Based on AJCC Stages to DecisionDx Classes in the Gerami Validation Cohort

AJCC Stage	DecisionDx Class	
	Class 1 (Low Risk), N (row%)	**Class 2 (High Risk), N (row %)**	**Total**

0	0	0	
Total stage I	50 (89%)[a]	6 (11%)	56
IA	37	1	
IB	10	5	
Total stage II	10 (29%)	24 (71%)	34
IIA	5	8	
IIB	5	12	
IIC	0	4	
Total stage III	1 (8%)	11 (92%)	12
Total stage IV	0 (0%)	2 (100%)	2
Total	61	43	104

Adapted from Gerami et al (2015)[41]
AJCC: American Joint Committee on Cancer
[a] The subclass for n=3 class 1 samples are not reported

Zager et al (2018) reported results of a second clinical validity study including AJCC stage I, II, or III primary melanoma tumors from 16 U.S. sites.[43] The samples were independent of the other validation studies. Of the 601 cases submitted from the institutions, 523 were included in the analysis (357 stage I/II). The excluded samples did not meet pre- and post-analytic quality control thresholds. SLN status was untested in 36% of the patients, negative in 34%, and positive in 30%. The report did not describe any adjuvant therapy that the patients received. Overall, 42 (13%) recurrence events occurred in DecisionDx class 1 patients and 100 (48%) recurrence events occurred in DecisionDx class 2 patients. The 5-year RFS estimated by Kaplan-Meier was 88% (95% CI, 85% to 92%) in class 1 and 52% (95% CI, 46% to 60%) in class 2. The reported sensitivity and specificity were 70% (95% CI, 62% to 78%) and 71% (95% CI, 67% to 76%), respectively, with a PPV of 48% (95% CI, 41% to 55%) and a NPV of 87% (95% CI, 82% to 90%). For comparison, the performance characteristics for 5-year RFS for sentinel lymph node status among those with SLNB were: sensitivity, 66% (95% CI, 57% to 74%); specificity, 65% (95% CI, 58% to 71%); PPV, 52% (95% CI, 44% to 60%); and NPV, 76% (95% CI, 69% to 82%). Estimates stratified by AJCC stage I or II are shown in Table 10. The reclassification of patients based on SLNB status using DecisionDx classes is shown in Table 12. If DecisionDx were used as a triage test such that only class 2 received SLNB, then 159 class 1 patients would not have undergone SLNB. Of the 159 patients in class 1, 56 were SLNB-positive and were therefore eligible for adjuvant therapy. It is not clear if the SLNB-positive patients in this study received adjuvant therapy. Of the 56 patients who were DecisionDx class 1 and SLNB-positive, 22 recurrence events occurred by 5 years.

Relevance, design, and conduct gaps are summarized in Tables 13 and 14.

Table 12. Reclassification of Patients Based on SLNB Status to DecisionDx Classes

SLNB	DecisionDx Class 1 (Low Risk)			DecisionDx Class 1 (High Risk)			Total
	n (%)	Events	5-Year RFS (95% CI), %	n (%)	Events	5-Year RFS (95% CI), %	
Negative	103 (65)	15	87 (81 to 94)	77 (43)	28	67 (57 to 79)	180
Positive	56 (35)	22	(61 (49 to 76)	101 (57)	60	37 (28 to 49)	157
Total	159			178			337[a]

Adapted from Zager et al (2017)[42]
RFS: recurrence-free survival; SLNB: sentinel lymph node biopsy.
[a] 337 patients had DecisionDx results and SLNB results.

Greenhaw et al (2018) reported results of an independent study of the DecisionDx test using their institution's melanoma registry and including patients who had been treated for cutaneous melanoma within the last 5 years and undergone DecisionDx testing.[57] Study characteristics and results were reported in the preceding Tables 9 and 10. Two-hundred fifty-six patients were tested; 84% were categorized as DecisionDx class 1 (low-risk) and 16% were DecisionDx class 2 (high-risk). 219 (86%) of tumors were AJCC stage I and 37 (14%) were AJCC stage II. None of the 18 stage I/class 2 tumors metastasized but 1 (0.5%) of 201 stage I/class 1 tumors metastasized. Ten (42%) of the stage II/class 2 tumors metastasized and 2 (15%) of the 13 stage II/class 1 tumors metastasized.

Keller et al (2019) reported results of a validity study including 159 patients (ages 26 to 88) diagnosed with melanoma 2013 and 2015 who underwent SNB and concurrent GEP testing.[58] Study characteristics and results were reported in the preceding Tables 9 and 10. 117 patients were classified as class 1 (91 subclass 1A and 26 subclass 1B) and 42 were classified as Class 2 (12 subclass 2A and 30 subclass 2B). 78% of the tumors were AJCC stage I, 13% were stage II, and 9% were stage III. Five-year RFS was reported only in a figure and sample sizes at year 5 and precision estimates were not included. There were 6 recurrent events (n=117) in class I patients by 3 years (3 year RFS, 97% [95% CI, 93 to 100]). There were 23 recurrent events (n=42) in class 2 patients (3 year RFS, 47% [95% CI, 34 to 65]). GEP class was significantly associated with RFS in multivariate analysis controlling for age, Breslow thickness, ulceration and SNB results.

Table 13. Clinical Validity Study Relevance Gaps of the DecisionDx Test

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of F/U
Gerami et al (2015); Validation subset	4. Study population includes AJCC stage III/IV lesions (13%), although analysis for only stage I/II was provided	1. Risk threshold for classification into class 1 or 2 not provided.	3. Not compared to other prediction tools	2. Evidence-based treatment or surveillance pathway using the test is not described	
Zager et al (2018)	4. Study population includes AJCC stage III lesions (32%), although analysis for only stage I/II was provided			2. Evidence-based treatment or surveillance pathway using the test is not described	
Greenhaw et al (2018)			3.Not compared to other prediction tools	2.Evidence-based treatment or surveillance pathway using the test is not described	1.Only 20 patients had 5-y follow-up
Keller et al (2019)				2: Evidence-based treatment or surveillance pathway using the test is not described	1. Unclear how many patients had 5 year follow-up

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. AJCC: American Joint Committee on Cancer.
F/U: follow-up
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 14. Clinical Validity Study Design and Conduct Gaps of the DecisionDx Test

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Completeness of F/U[e]	Statistical[f]
Gerami et al (2015); Validation subset	2. Not consecutive or random		1. Time between collection of biopsy and DecisionDx not described	1. No registration reported	1. No description of number of samples (if any) that failed to produce results or were indeterminate	1. CIs not reported but were calculated based on data provided
Zager et al (2018)	2. Not consecutive or random		1. Time between collection of biopsy and DecisionDx not described	1. No registration reported	1. No description of number of samples (if any) that failed to produce results or were indeterminate	
Greenhaw et al (2018)			1.Some samples collected after treatment	1.No registration reported		
Keller et al (2019)				1. No registration reported		1. Estimates and CIs at year 5 were not provided.

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Follow-Up key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

In a subsequent analysis of patients with melanoma who had undergone SLNB, Gerami et al (2015) compared prognostic classification by DecisionDx-Melanoma with biopsy results.[59] A total of 217 patients comprised a convenience sample from a database of 406 patients previously tested with DecisionDx-Melanoma. Patients who had undergone SLNB appear to overlap with patients in Gerami et al (2015)[42] discussed previously. Most (73%) patients had a negative SLNB, and 27% had a positive SLNB. DecisionDx-Melanoma classified 76 (35%) tumors as low risk (class I) and 141 (65%) tumors as high risk (class II). Within the group of SLNB-negative patients, the 5-year overall survival rate was 91% in class I patients and 55% in class II patients. Within the group of SLNB-positive patients, the 5-year overall survival rate was 77% in class I patients and 57% in class II patients.

Ferris et al (2017) compared the accuracy of DecisionDx-Melanoma with the web-based AJCC Individualized Melanoma Patient Outcome Prediction Tool.[60] The study included 205 patients who appear to overlap with the patients in the second Gerami et al (2015) study described above. AJCC-predicted 5-year survival for each patient was categorized into low and high risk based on both a 68% predicted 5-year survival and a 79% predicted 5-year survival. The 68% and 79% cut points were reported to correspond to 5-year survival in patients with stage IIA and IIB, respectively, although it is unclear whether those cut points were prespecified, whether they were based on internal or external estimates of risk, or whether they are commonly used in practice. The prognostic sensitivity and specificity for death (median follow-up, 7 years) of the Decision-Dx Melanoma were 78% and 69%, respectively (CIs not reported). The sensitivity and specificity for the AJCC calculator with the 79% cut point were 60% and 74%, respectively. The combination of the DecisionDx-Melanoma and AJCC tools had a sensitivity of 82% and specificity of 62%. The cross-classification for the DecisionDx-Melanoma and AJCC tools for 5-year overall survival is shown in Table 15.

Table 15. Cross-Classification for the DecisionDx-Melanoma and AJCC Tool (79% Cut point) for 5-Year Overall Survival

Risk Classification (DecisionDx-Melanoma vs. AJCC)	n	No. of Events	5-Year Overall Survival, %
Low/low	105	9	96
Low/high	13	2	83
High/low	30	11	71
High/high	57	28	44

Adapted from Ferris et al (2017)[27]
AJCC: American Joint Committee on Cancer

Clinical Useful

A test is clinically useful if the results inform management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No direct evidence of clinical utility was identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Decision-impact studies have been published reporting on the impact of DecisionDx on physicians' management decisions.[61-66] Given the lack of established clinical validity and no reported long-term outcomes; it is not known whether any management changes were clinically appropriate.

For the proposed use of the test as a triage for SLNB (identify patients who can avoid SLNB), performance characteristics are not well-characterized.

For the proposed use of the test as a replacement for SLNB (identify patients who are AJCC stage I/II who should receive adjuvant therapy), an evidence-based management pathway would be needed to support the chain of evidence. The existing RCTs demonstrating that adjuvant therapy reduces recurrence included node positive patients.

No evidence was identified that demonstrated that adjuvant therapy or increased surveillance improves net health outcomes in AJCC stage I or II patients who are DecisionDx class 2.

Section Summary: Gene Expression Profiling to Guide Management Decisions in Melanoma

To use prognostic information for decision-making, performance characteristics should be consistent and precise. Two independent studies, using archived tumor specimens, have reported 5-year RFS in AJCC stage I or II patients. If the test is to be used to select stage I and II patients for adjuvant therapy or enhanced surveillance then it should identify a group with high risk of recurrence. Gerami et al (2015) reported RFS rates of 37% for DecisionDx class 2 (high-risk) in patients in AJCC stage I and II patients. However, 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. In addition, to 'rule-in' patients for additional treatment or surveillance, the test should have specificity and PPV. In Zager et al (2018) and Greenhaw et al (2018) the specificities were 71% and 87%, respectively, while the PPV were only 48% and 24%, respectively. The low 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 or 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).

If the test is to be used to select stage I and II patients who can avoid SLN biopsy, then it should identify a group who are eligible for SLN biopsy but have low risk of recurrence. 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 (2018) reported RFS rates of 96% (95% CI, 94% to 99%) for DecisionDx class 1 in patients with AJCC stage I disease and 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 in either DecisionDx risk group as evidenced by the variation in estimates across studies. These studies do not report 5-year RFS in the specific population in which the manufacturer is suggesting utility for guiding SLN biopsy (i.e., Class 1A patients ≤55 years old who have tumors less than 2 mm deep [T1-T2]). Data on 5-year RFS is not available for this target population outside of the Vetto (2019) retrospective cohort that was used to develop the target population.

Zager et al (2017) also reported that 56 of 159 (35%) patients who were DecisionDx class 1 (low-risk) were SLN biopsy-positive and in those patients 22 recurrences (39%) occurred over 5 years.[43.] 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.

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, with respect to the proposed uses of identifying higher-risk patients that should receive adjuvant therapy or enhanced surveillance, 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 or surveillance.

There is no direct evidence of clinical utility. A chain of evidence for clinical utility cannot be created due to lack of robust evidence of clinical validity and lack of evidence-based management pathway.

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 diagnostic yield of early stage melanoma on biopsied tissue is limited. Histopathologic assessment of early stage biopsied melanoma tissue is challenging and has significant discordance between pathologists. While fellowship-trained board certified dermatopathologists tend to have a higher accuracy than other pathologists, under-interpretation is likely. Conventional melanoma care may lead to both biopsies of non-malignant lesions, and even in those patients who do have a biopsy the diagnosis of a malignancy may be missed. As such, there is potential clinical utility for a test that can either spare a patient the need for a biopsy. The Pigmented Lesion Assay (PLA) was developed to fill the niche of reducing the biopsy rate of non-malignant lesions. The evidence is sufficient 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 2 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 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 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% 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 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. 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 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% 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 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 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. 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.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATMENTS

National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines (v.2.2024) for melanoma made the following statements on use of gene expression profiling.[64] The guidelines state the following regarding diagnostic testing for indeterminate melanocytic neoplasms following histopathology: "Melanocytic neoplasms of uncertain biologic potential present a unique challenge to pathologists and treating clinicians. Ancillary methods to aid in benign versus malignant differentiation include molecular cytogenetics (e.g., comparative genomic hybridization [CGH]), fluorescence in situ hybridization [FISH]), gene expression profiling (GEP), next generation sequencing (NGS), and immunohistochemistry (IHC), among others. While limited report on the intermediate category of melanocytic neoplasia show evolutionary pathogenic genetic alteration during melanoma progression, there are insufficient data from histologically ambiguous melanocytic neoplasms."

The guidelines state the following regarding prognostic testing:

- “The use of gene expression profiling (GEP) testing according to specific AJCC-8 melanoma stage (before or after sentinel lymph node biopsy [SLNB]) requires further prospective investigation in large, contemporary data sets of unselected patients. Prognostic GEP testing to differentiate melanomas at low versus high risk for metastasis should not replace pathologic staging procedures. Moreover, since there is a low probability of metastasis in stage I melanoma and a higher proportion of false-positive results, GEP testing should not guide clinical decision-making in this subgroup."
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- “Various studies of prognostic GEP testing suggest its role as an independent predictor of worse outcomes, though not superior to Breslow thickness or SLN status. It remains unclear whether available GEP platforms are reliably predictive of outcomes across the risk spectrum of melanoma . Prospective validation studies similar to those performed in breast cancer) are required to define the clinical utility of molecular testing more accurately prior to widespread implementation of GEP for prognostication of cutaneous melanoma and in particular to determine its role in guiding surveillance imaging, SLNB, and adjuvant therapy.’
- "Existing and emerging GEP tests and other molecular techniques (i.e., circulating tumor DNA tests) should be prospectively compared to determine their clinical utility, including with no-cost, contemporary multivariable SLNB risk prediction models."

American Academy of Dermatology

The American Academy of Dermatology (2019) published guidelines of care for the management of primary cutaneous melanoma.[65] 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 (e.g., 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 (e.g., sentinel lymph node eligibility, follow-up, and/or therapeutic choice) is not recommended outside of a clinical study or trial."

In 2019, the American Academy of Dermatology updated their Choosing Wisely recommendation that physicians not perform sentinal lymph node biopsy or other diagnostic tests for the evaluation of early, thin melanoma because they do not improve survival.[66.] The Academy noted that early, thin melanoma (melanoma in situ, T1a melanoma or T1b melanoma $\leq$ 0.5 mm) has a very low risk of the cancer spreading to the lymph nodes or other parts of the body and a 97% 5-yr survival rate.

National Society for Cutaneous Medicine

In 2019, the National Society for Cutaneous Medicine published appropriate use criteria for the integration of diagnostic and prognostic gene expression profile assays for management of cutaneous melanoma.[67] The criteria were developed with "unrestricted educational grants from related companies involved with these technologies". The majority of the panel members were consultants or advisors for Castle BioSciences or Myriad. The criteria were consensus-based using a modified Delphi approach. Numerous recommendations were made for each of the tests reviewed here. Some of the recommendations are as follows:

- Using PLA test for patients with atypical lesions requiring assessment beyond visual inspection to help in selection for biopsy (B = Inconsistent or limited quality patient-oriented evidence)
- Using myPath for differentiation of a nevus from melanoma in an adult patient when the morphologic findings are ambiguous by light microscopic parameters (A = Consistent, good-quality patient-oriented evidence)
- Using DecisionDx by integrating results into the decision to adjust follow up regimens or to assess need for imaging (B = Inconsistent or limited quality patient-oriented evidence)
- Using DecisionDx by integrating results into subsequent management of patients:

- Who are sentinel node negative (A = Consistent, good-quality patient-oriented evidence)
- Who are in AJCC “low risk” categories: (Thin (<1mm), Stage I-IIA, SLNBx-) (B= Inconsistent or limited quality patient-oriented evidence)

- Using DecisionDx by integrating 31GEP results as a criteria for inclusion in a chemotherapy regimen (C = Consensus, disease-oriented evidence, usual practice, expert opinion, or case series)

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov did not identify any ongoing or unpublished trials that would likely influence this review.

Government Regulations
National:
There is no national coverage determination

Local:
LCD L38178: MolDX: Pigmented Lesion Assay. For services on or after 12/28/2023.
The PLA is indicated only for use on pigmented skin lesions, for which a diagnosis of melanoma is being considered. The test may only be ordered by clinicians who evaluate pigmented skin lesions and perform biopsies. The test is covered for use as a source of information on whether or not to perform a biopsy.
The specific characteristics that the lesion must have are as follows:

- The lesion must meet one or more ABCDE criteria (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 already clinically diagnosed as melanoma or for which the clinical suspicion is sufficiently high that the treating clinician believes melanoma is a more likely diagnosis than not
- Lesions in areas other than palms of hands, soles of feet, nails, mucous membranes and hair covered areas that cannot be trimmed

Additional coverage requirements:

- The ordering clinician must also have a plan at the time of ordering the test to continue to monitor the skin lesion for changes if the test is negative. The record must also contain a photograph of the lesion at the time that the PLA is ordered to allow for appropriate evaluation in subsequent follow-up.
- Records must clearly support that the ordering clinician has the knowledge, skills, and experience to evaluate and biopsy pigmented skin lesions. If this information is not contained with the chart of the beneficiary to whom a service is being rendered, it must be supported by other readily available documentation, such as credentialing documentation, or documentation of training in the performance of such tasks. Such documentation should be provided if there are documentation requests.
- The ordering physician must clearly document the lesion site on the patient’s body
- The test may not be ordered for the same lesion a second time.

- Only 1 test may be used per patient per clinical encounter, in most cases. In roughly 10% of patients, a second test may be indicated for the same clinical encounter. For rare cases where more than 2 tests are indicated in a single clinical encounter, an appeal with supporting documentation may be submitted for additional tests.

LCD L38018: MolDX: Melanoma Risk Stratification Molecular Testing. Effective for services performed on or after 7/3/2022.[64]

Molecular diagnostic tests used to assist in risk stratification of melanoma patients are covered when:

1. The patient has a personal history of melanoma AND:
    a. Either:
        i. Has Stage T1b and above OR
        ii. Has T1a with documented concern about adequacy of microstaging
    b. Is undergoing workup or being evaluated for treatment, AND
    c. Does not have metastatic disease AND
    d. Presumed risk for a positive Sentinel Lymph Node Biopsy (SLNB) based on clinical, histological, or other information is >5% AND
    e. Has a disease stage, grade, and Breslow thickness (or other qualifying conditions) within the intended use of the test
2. The TEST has demonstrated, as part of a Technical Assessment:
    a. Clinical validity of analytes tested in predicting metastatic disease in peer-reviewed scientific literature
    b. Utility beyond clinical, histological, and radiographical factors in the ability to accurately stratify patients into risk groups to manage patient care
    c. Appropriate analytical validity
    d. Performance characteristics equivalent to other covered, similar tests

LCD L37923: MolDX: my Path Melanoma Assay. Published 6/10/19, last updated 12/30/21. Retired 08/12/2023.
This Medicare contractor will provide limited coverage for the myPath® ;Melanoma assay (Myriad Genetic Laboratories, Salt Lake City, UT; Z-Code ZB041) 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.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing—for Familial Cutaneous Melanoma, CDKN2A
- Genetic Testing—Gene Expression Profiling for Uveal Melanoma

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through April 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/19	10/16/18	10/16/18	Joint policy established
1/1/20	10/15/19		Routine policy update, rationale section updated, references 51-54 and 62-64 added. No change in policy statement.
1/1/21	12/11/20		Rationale updated, references 54, 56 and 66 added. No change in policy status.
7/1/21	4/20/21		Added code 81529 as E/I effective 1/1/21.
7/1/22	4/19/22		Routine policy maintenance, no change in policy status. Added references #63 and 66. Added code 0314U as E/I.
1/1/23	10/18/22		Added code 0089U as E/I representing the Pigmented Lesion Assay (PLA). Rationale updated, reference #35 added. No change in policy status.
9/1/23	6/13/23		Status changed from E/I for DermTech to established with criteria. Code 0089U was moved to established, code 81479 (NOC) was added to E/I codes. Added references 70 & 71.Vendor managed: NA. (ds)
7/1/24	4/22/24		Routine policy maintenance, reviewed materials from Castle Biosciences. Vendor managed: N/A. (ds)

Next Review Date: 2nd Qtr. 2025

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:

BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENE EXPRESSION PROFILING FOR CUTANEOUS MELANOMA

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.