2.04.146	Gene Expression Profiling for Cutaneous Melanoma		
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Policy Statement

I. Gene expression testing, including but not limited to the Pigmented Lesion Assay, in the evaluation of individuals with suspicious pigmented lesions is considered **investigational**.

II. Gene expression testing, including but not limited to the myPath Melanoma test, in the evaluation of individuals with melanocytic lesions with indeterminate histopathologic features is considered **investigational**.

III. Gene expression testing, including but not limited to DecisionDx-Melanoma, in the evaluation of individuals with cutaneous melanoma is considered **investigational** for all indications.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Genetic Counseling
Experts recommend formal genetic counseling for individuals who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some individuals; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Description

Laboratory tests have been developed that detect the expression of different genes in pigmented lesions or melanoma tumor tissue. Test results may help providers and patients decide whether to biopsy suspicious pigmented lesions, aid in diagnosis lesions with indeterminate histopathologic lesions or determine whether to perform sentinel lymph node biopsy in patients diagnosed with stage I or II cutaneous melanoma. This report summarizes the evidence of 3 tests.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these

instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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.

Rationale

Background

Cutaneous Melanoma

Cutaneous melanoma accounts for more than 90% of cases of melanoma.[1,] For many decades, melanoma incidence was rapidly increasing in the U.S. However, recent estimates have suggested the rise may be slowing. In 2018, more than 90,000 new cases of melanoma are expected to be diagnosed, and more than 9000 people are expected to die of melanoma.[2,]

Risk Factors

Exposure to solar ultraviolet radiation is a major risk factor for melanoma. Most melanomas occur on the sun-exposed skin, particularly those areas most susceptible to sunburn. Likewise, features that are associated with an individual's sensitivity to sunlight, such as light skin pigmentation, red or blond hair, blue or green eyes, freckling tendency, and poor tanning ability are well-known risk factors for melanoma.[3,4,] There is also a strong association between high total body nevus counts and melanoma.[5,]

Several genes appear to contribute to melanoma predisposition such as tumor suppressor gene *CDKN2A*, melanocortin-1 receptor (*MC1R*) gene, and *BAP1* variants.[6,7,8,] Individuals with either familial or sporadic melanoma have 2 to 3 times increased risk of developing a subsequent primary melanoma.[9,] Several occupational exposures and lifestyle factors, such as body mass index and smoking, have been evaluated as possible risk factors for melanoma.[10,]

Gene Expression Profiling

Gene expression profiling (GEP) measures the activity of thousands of genes simultaneously and creates a snapshot of cellular function. Data for GEP are generated by several molecular technologies including DNA microarrays that measure activity relative to previously identified genes and RNA-Seq that directly sequences and quantifies RNA molecules. Clinical applications of GEP include disease diagnosis, disease classification, prediction of drug response, and prognosis.

Literature Review

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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Gene Expression Profiling to Guide Initial Biopsy Decisions

Clinical Context and Test Purpose

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

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

- **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 1 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 gene expression profiling (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 1 or more ABCDE criteria.

Interventions

The test being considered is the DermTech Pigmented Lesion Assay. The Pigmented Lesion Assay 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 Pigmented Lesion Assay was first

described in Wachsman et al (2011) and Gerami et al (2014).[16,17,] and development of the specific Pigmented Lesion Assay 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 Pigmented Lesion Assay test report includes 2 results. The first result is called the Pigmented Lesion Assay 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 Pigmented Lesion Assay score that ranges from 0 to 100, with higher scores indicating higher suspicion of malignant disease.[15,]

It is not clear whether the Pigmented Lesion Assay test is meant to be used as a replacement, triage, or add-on test with respect to dermoscopy. The Pigmented Lesion Assay 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 the 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 U.S. 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 a 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 the diagnosis of cancer. A longer follow-up would be necessary to determine the effects on overall survival.

Study Selection Criteria

For the evaluation of clinical validity of the Pigmented Lesion Assay 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.

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 from 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,]

Review of Evidence

Observational Studies

Studies were excluded from the evaluation of the clinical validity of the Pigmented Lesion Assay test because they reported results of the development cohort,[17,] they did not use the marketed version of the test,[16,17,] did not include the reference standard test on Pigmented Lesion Assay negative patients,[23,] did not adequately describe the patient characteristics,[24,] or did not adequately describe patient selection criteria.[24,]

The validation cohort from the Gerami et al (2017) publication was included.[18,] The study characteristics are described in Table 1. The report stated that included lesions were selected by dermatologists experienced in pigmented lesion management from 28 sites in the U.S., Europe, and Australia; therefore, the samples were likely not consecutive or random. Information regarding the previous testing was not provided. The flow of potential and included samples was not clear, and whether the samples were all independent or multiple samples from the same patient were not described. Diagnosis of melanoma was based on consensus among a primary reader and 3 expert dermatopathologists. The report did not state whether the histopathologic diagnosis was blinded to the results of the Pigmented Lesion Assay test but did state the diagnosis was "routinely" assessed. Interpretation of the Pigmented Lesion Assay result does not depend on a reader, so it is blinded to histopathologic results. In 11% of cases originally selected, a consensus diagnosis was not reached, and these samples were not included in the training or validation cohorts. Dates of data collection were not reported. Sex and anatomic location of biopsy were reported, but other clinical characteristics (e.g., risk factors for melanoma, presenting symptoms) were not. Study results are shown in Table 2. The study training cohort included 157 samples with 80 melanomas and 77 non-melanomas. The study validation cohort included 398 samples with 87 melanomas and 311 non-melanomas. Study relevance, design, and conduct gaps are in Tables 3 and 4.

Table 1. Clinical Validity Study Characteristics of the Pigmented Lesion Assay 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 ≥4	Retrospective Not	Histopathology; consensus diagnosis	Quantitative PCR yielded an amplification curve	PLA patch before surgical biopsy; timing	Not clear

Study	Study Population	Design	Reference Standard for Dx of Melanoma	Threshold Score for PLA Test	Timing of Reference and PLA Tests	Blinding of Assessors
	mm in diameter Without obvious or suspicious nodular melanoma 24% from extremities, 13% from the head and neck, 62% from the trunk 55% of samples from men Median age, 49 y (range, 19 to 97 y)	consecutive or random		and a measurable cycle threshold value Either *LINC00518* or *PRAME* detected	between the patch and surgical biopsy unclear	

Dx: diagnosis; PCR: polymerase chain reaction; PLA: Pigmented Lesion Assay.

Table 2. Clinical Validity Study Results of the Pigmented Lesion Assay 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 not provided in the report; calculated from data provided.

Table 3. Clinical Validity Study Relevance Limitations of the Pigmented Lesion Assay 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 limitations 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 Limitations of the Pigmented Lesion Assay 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 limitations 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 (RCTs).

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 Pigmented Lesion Assay 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 Pigmented Lesion Assay test results and, in the second round, dermatologists had access to Pigmented Lesion Assay test results with the order of cases being scrambled. The dermatologists were asked whether the lesions should be biopsied after each round. Therefore, the corresponding number of biopsy decisions should be 45×60×2=5400. Data were collected in 2014 and 2015. Results were reported for 4680 decisions with no description of the disposition of the remaining decisions. Of the 4680 reported decisions, 750 correct biopsy decisions were made without Pigmented Lesion Assay results while 1331 were made with Pigmented Lesion Assay results and 1590 incorrect biopsy decisions were made without Pigmented Lesion Assay results while 1009 incorrect biopsy decisions were made with Pigmented Lesion Assay results.

Section Summary: Gene Expression Profiling to Guide Initial Biopsy Decisions

Multiple high-quality studies are needed to establish the clinical validity of a test. The Pigmented Lesion Assay test has 1 clinical validity study with many methodologic and reporting limitations. Therefore, performance characteristics are not well-characterized. Also, the test has not been compared with dermoscopy, another tool frequently used to make biopsy decisions. There is no direct evidence of clinical utility. A chain of evidence for clinical utility cannot be constructed due to lack of robust evidence of clinical validity.

Gene Expression Profiling 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. The myPath report also classifies these scores: -16.7 to -2.1 are “benign”; -2.0 to -0.1 are “indeterminate”; and 0.0 to +11.1 are “malignant”. The development of the test has been described by Clarke et al (2015).[25,]

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[,25,26,27,] 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 diagnose 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 2 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 to 156 months) and reported a FISH sensitivity of 60% and a specificity of 50% for development of metastases during follow-up.[28,] 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 to 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.[29,]

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 many years after the treatment of melanoma. In the 2 studies evaluating long-term outcomes of FISH (described above), the mean follow-up was approximately 5.5 and 9 years.[28,29,] In Vergier et al (2011), metastases in the FISH-negative group generally occurred within 5 years.[29,]

For this section of the review, at least 5 years of event-free follow-up is required to confirm negative tests. The event of interest is metastasis.

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 (clinical outcome with at least 5 years of follow-up for negatives);
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

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).

Review of Evidence

Observational Studies

Studies were excluded from the evaluation of the clinical validity of the myPath test because authors did not use the specified reference standard of long-term (at least 5 years) follow-up[25,26,30,31,32,27,] and/or did not adequately describe patient characteristics.[25,]

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.[33,] 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 US 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 7 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.[34,] 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 Predicting Metastasis

Study	Study Population	Design	Reference Standard	Threshold Score for Positive myPath Test	Timing of Reference and myPath Tests	Blinding of Assessors
Ko et al (2017)[33,]	Primary cutaneous melanomas or benign melanocytic nevi Mean age, 53 y 55% of samples from men	Retrospective Not consecutive or randomly selected	Positive: malignant lesions that produced distant metastases Negative: Event-free follow-up, recommended 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)[34,]	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	Scores from 0.0 to 11.1 (i.e., "likely malignant")	Retrospective testing using archived samples.	Yes

Study	Study Population	Design	Reference Standard	Threshold Score for Positive myPath Test	Timing of Reference and myPath Tests	Blinding of Assessors
			outcome was defined as absence of local recurrence or metastases throughout a protracted clinical follow-up period (5-year follow-up was not required).			

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)[33,]	240	175	58 failed to produce test result 7 with indeterminate 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)[34,]	182	125	56 not considered to be diagnostically uncertain; 1 missing slide	44.1%	90.4 (79.0 to 96.8)	95.5 (87.3 to 99.1)	94.0 (83.8 to 97.9)	92.7 (84.6% to 96.7)

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 Limitations of the myPath Test

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Ko et al(2017)[33,]	4. Study population is not limited to lesions that are indeterminate following histopathology				None noted
Clarke et al (2020)[34,]					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 study limitations 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 8. Clinical Validity Study Design and Conduct Limitations 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)[33,]	2. Samples not consecutive or random		1. Unclear how much time elapsed between biopsy and myPath test	1. No registration reported	2. More than 25% of samples tested did not produce results or produced indeterminate results	1. CIs for sensitivity and specificity are not reported but were calculated based on data provided. NPV, PPV were not reported
Clarke et al (2020)[34,]	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 limitations 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 RCTs.

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.[35,36,] Given the lack of health 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 2 clinical validity studies including long-term follow-up for metastasis as the reference standard. In 1 study, it is not clear whether the study population included lesions that were indeterminate following histopathology. The second study focused on indeterminate lesions but had limitations including a retrospective design and less than 5-year follow-up in 31% of cases. Therefore, performance characteristics are not well-characterized. 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.

Gene Expression Profiling 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 (AJCC) tumor, node, metastasis staging system.[37,]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. Individuals may also undergo sentinel lymph node (SLN) 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, individuals with AJCC stage I or II (node-negative) melanoma do not generally receive adjuvant therapy. Individuals with higher risk melanoma receive adjuvant immunotherapy or targeted therapy. Ipilimumab has been shown to prolong recurrence-free survival (RFS) by approximately 25% compared with placebo at a median of 5.3 years in individuals with resected, stage III disease.[38,] Nivolumab has been shown to further prolong survival compared with ipilimumab by approximately 35% at 18 months.[39,] 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.[40,]

Patients with stage I and IIA disease should undergo an annual routine physical and dermatologic examination. These patients typically do not receive surveillance imaging. Patients with stage IIB to III melanoma may be managed with more frequent follow-up and imaging surveillance following therapy. However, follow-up strategies and intervals are not based on rigorous data, and opinions vary regarding appropriate strategies.

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

At least 3 uses for the test have been suggested. One clinical validity study (described below), the authors stated that "high-risk individuals with stage I and II disease may benefit from adjuvant therapy and/or enhanced imaging protocols to allow for early detection of metastasis."[41,] In another clinical validity study, the authors concluded that the test's "role in consideration of individuals for adjuvant therapy should be examined prospectively."[42,] This use of the test would be as a replacement for SLN biopsy since SLN biopsy is currently used to identify individuals clinically diagnosed as stage I and II who have node involvement and are candidates for adjuvant therapy.

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 to 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 SLN biopsy (i.e., a triage test for SLN biopsy).
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 is individuals with AJCC stage I/II cutaneous melanoma.

To select individuals for enhanced surveillance and referrals, the relevant population of interest is individuals with AJCC stage I to III cutaneous melanoma.

To select individuals who can avoid SLN biopsy, the relevant population of interest is individuals with AJCC stage I or II cutaneous melanoma who are being considered for SLN biopsy. The manufacturer's website says the test is for 'eligible patients 55 years of age and older who have tumors less than 2 mm deep (T1 to T2)'

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.

The development of the test was described in Gerami et al (2015).[41,] To develop the DecisionDx-Melanoma gene panel, Gerami et al conducted a meta-analysis of published studies that identified differential gene expression in metastatic versus 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 SLN biopsy. Information about treatments received was not provided.

The DecisionDx test report provides a 'class' which stratifies tumors as class 1 or class 2. According to the sample report available on the manufacturer's website: "The DecisonDx-Melanoma algorithm generates a value between 0 and 1 with a crossover point of 0.5. Subclassification (A or B) is based on proximity of this value to the crossover point."

Comparators
Treatment and surveillance recommendations are based on AJCC staging. SLN biopsy 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 and National Comprehensive Cancer Network have similar but not identical recommendations regarding which patients should undergo SLN biopsy based on thickness and other high-risk features.

SLN biopsy has a low rate of complications; in the Sunbelt Melanoma Trial, a prospective multi-institutional study of SLN biopsy for melanoma reported by Wrightson et al (2003), less than 5% of the 2120 patients developed major or minor complications associated with SLN biopsy.[43,]
Online tools are available to predict prognosis based on the AJCC guidelines. The original AJCC tool was developed by Soong et al (n.d.).[44,] Callender et al (2012) incorporated SLN biopsy results into a revised tool (http://www.melanomacalculator.com/).[45,]

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

If the test is used to 'rule-in' a higher risk for recurrence or metastasis 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 enhanced surveillance.

Regarding patients who would benefit from enhanced surveillance in AJCC stage IIB to III patients:
If the test is used to "rule-in" risk for recurrence or metastasis in AJCC stage IIB to III patients, a positive DecisionDx (class 2) would indicate that a patient might benefit from enhanced surveillance. Therefore, the potential beneficial outcomes of a true positive result are additional surveillance and potentially prolonged survival. The potential harmful outcomes of a false-positive result are unnecessary adverse effects and burdens of enhanced surveillance.

If the test is used to 'rule-out' an increased risk for recurrence or metastasis in AJCC stage IIB to III patients, a negative DecisionDx (class 1) test result would indicate that a patient might be able to avoid enhanced surveillance. Therefore, the potential beneficial outcomes of a true negative result are avoiding burdens of surveillance and potential overtreatment. The potential harmful outcomes of a false-negative result are reduced treatment and increase in mortality.

The potential benefit of a true negative test is avoiding the burden of surveillance and potential overtreatment. The potential harmful outcomes of a false-negative result are reduced treatment and increase in mortality.

Regarding selecting AJCC stage I to IIA patients who can avoid SLN biopsy:
For patients meeting guideline-recommended criteria for SLN biopsy, a positive DecisionDx (class 2) test result would not change outcomes. The patients would proceed to SLN biopsy, as they would have without the DecisionDx test, and treatment and imaging decisions would depend on SLN biopsy results. A negative DecisionDx (class 1) test result in patients 55 years of age and older who have tumors less than 2 mm thick (T1 to T2) would indicate that a patient could avoid an SLN biopsy. Therefore, the potential beneficial outcomes of a true-negative result are avoidance of an SLN biopsy and related adverse effects and burdens. The potential harmful outcomes of a false-negative result are reduced time to recurrence due to not identifying node-positive patients that would be eligible for beneficial adjuvant treatment and potentially reduced survival.

The risk of recurrence decreases over time but does not reach 0. 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. Five-year RFS is the outcome and time-point of interest.

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 or 5-year metastasis-free survival [MFS]);
- Patient/sample clinical characteristics were described

- Patient/sample selection criteria were described.

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).

Review of Evidence

Observational Studies

Several papers were excluded from the evaluation of clinical validity. Hsueh et al (2017), Podlipnik et al (2019), and Hsueh et al (2021) were excluded from the evaluation of the clinical validity of the DecisionDx test because they did not report 5-year outcomes (median follow-up, 1.5 years, 2 years, and 3.2 years, respectively).[49,50,51,] Samples used in Gerami et al (2015)[41,] and Ferris et al (2017)[24,] appear to overlap with each other and will not be considered independent validation studies for inclusion in the tables. They are described briefly following the clinical validity tables. Data used in Gastman et al (2019) are stated to combine previous validation studies and included exploratory subgroup analysis.[52,53,41,42,] 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 without report of 5-year outcomes.[54,] Marks et al (2019) describes the development of a cutpoint.[55,]

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 DecisionDx Tests	Blinding of Assessors
Gerami et al (2015)[41,]; Validation subset	Adults Stage I to IV cutaneous melanoma (87% stage I/II) At least 5 y of FU (median, 7.0 y) Median Breslow thickness, 0.8 mm (nonmetastasis) and 3.99 mm (metastasis) SLN positivity NR	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)[42,]	Stage I to III cutaneous melanoma (68% stage I/II) At least 5 y of FU (median, 7.5 y) Median Breslow thickness, 1.2 mm 30% SLN positive	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)[56,]	Patients who were treated for primary invasive CM of any Breslow depth within	Retrospective Consecutive	5-y MFS	Commercial test cutoffs used	Institution offered DecisionDx testing to newly diagnosed and those treated	Yes

Study	Study Population	Design	Reference Standard / Outcome Measure	Threshold Score for Positive DecisionDx Test	Timing of Reference and DecisionDx Tests	Blinding of Assessors
	the last 5 years and had had GEP testing (86% stage I, 14% stage II) Mean follow-up of 23 months; only 20 patients had 5-year follow-up				within the previous 5 years	
Keller et al (2019)[57,]	Patients had CM (91% stage I/II), opted for GEP testing and underwent SLN biopsy 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 (5-y RFS reported in a figure only)	Commercial test cutoffs used	Patients diagnosed between 2013 and 2015 GEP reported to be performed concurrently with SLN biopsy	Yes

CM: cutaneous melanoma; GEP: gene expression profiling; FU: follow-up; NR: not reported; MFS: metastasis-free survival; RFS: recurrence-free survival; SLN: sentinal lymph node.

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 or MFS[a]		Sensitivity[a]	Specificity[a]	PPV[a]	NPV[a]
			Class 1	Class 2				
Gerami et al (2015)[41,]; 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) p<.001 vs class 1	89 (73 to 97)[b]	83 (72 to 91)[b]	72 (56 to 85)[b]	93 (84 to 98)[b]
AJCC stage I and II	Unclear/78		3 events RFS=98 (NR)	18 events RFS=37 (NR). p<.001 vs class 1	86 (64 to 97)[b]	84 (72 to 93)[b]	67 (46 to 83)[b]	94 (84 to 99)[b]
Zager et al (2018)[42,]		Did not meet analytic quality control thresholds						
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)

Study	Initial / Final N	Excluded Samples	Events and Kaplan-Meier 5-Year RFS or MFS[a]		Sensitivity[a]	Specificity[a]	PPV[a]	NPV[a]
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)[56,]	256 / 256	None excluded but only 20 had 5-year follow-up	3 events MFS=93 (82 to 100)	8 events MFS=69 (52 to 90)	77 (46 to 94)	87 (82 to 91)	24 (13 to 40)	99 (96 to 100)
Keller et al (2019)[57,]	159 / 174	15 patients had insufficient tumor for GEP testing	events unclear at year 5 RFS[c] ~ 97 (NR)	events unclear at year 5 RFS[c] ~ 40 (NR)	NR	NR	NR	NR

AJCC: American Joint Committee on Cancer; Dx: diagnosis; GEP: gene expression profiling; MFS: metastasis-free survival; 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.

[c] RFS at 5 years not provided in text but estimated from a figure

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).[41,] 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% (confidence intervals [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. Confidence intervals 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.[42,] 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 biopsy 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 SLN biopsy 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 SLN biopsy status using DecisionDx classes is shown in Table 12. If DecisionDx were used as a triage test such that only class 2 received SLN biopsy, then 159 class 1 patients would not have undergone SLN biopsy. Of the 159 patients in class 1, 56 were SLN biopsy-positive and were therefore eligible for adjuvant therapy. It is not clear if the SLN biopsy-positive patients in this study received adjuvant therapy. Of the 56 patients who were DecisionDx class 1 and SLN biopsy-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 SLN Biopsy Status to DecisionDx Classes

SLN Biopsy	DecisionDx Class 1 (Low-Risk)			DecisionDx Class 2 (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,]
CI: confidence interval; RFS: recurrence-free survival; SLN: sentinel lymph node.
[a] 337 patients had DecisionDx results and SLN biopsy 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.[56,] 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). Eighty-six percent (n=219) 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 in 2013 and 2015 who underwent SLN biopsy and concurrent GEP testing.[57,] Study characteristics and results were reported in the preceding Tables 9 and 10. One hundred seventeen 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). Seventy-eight percent 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 SLN biopsy results.

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

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Gerami et al (2015)[41]; 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.	3,4.Multivariate models included only control for AJCC stage. Reclassification not provided	2. Evidence-based treatment or surveillance pathway using the test is not described	
Zager et al (2018)[42],	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)[56],			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-year follow-up
Keller et al (2019)[57],				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 limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
AJCC: American Joint Committee on Cancer.
[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 Limitations of the DecisionDx Test

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Completeness of Follow-Up[e]	Statistical[f]
Gerami et al (2015)[41]; 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)[42],	2. Not consecutive or random		1. Time between collection of biopsy and DecisionDx	1. No registration reported	1. No description of number of samples (if any) that failed to produce results	

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Completeness of Follow-Up[e]	Statistical[f]
			not described		or were indeterminate	
Greenhaw et al (2018)[56,]			1. Some samples collected after treatment	1. No registration reported		
Keller et al (2019)[57,]				1. No registration reported		1. Estimates and CIs at year 5 were not provided.

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CI: confidence interval.
[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 SLN biopsy, Gerami et al (2015) compared prognostic classification by DecisionDx-Melanoma with biopsy results.[58,] A total of 217 patients comprised a convenience sample from a database of 406 patients previously tested with DecisionDx-Melanoma. Patients who had undergone SLN biopsy appear to overlap with patients in Gerami et al (2015)[41,] discussed previously. Most (73%) patients had a negative SLN biopsy, and 27% had a positive SLN biopsy. DecisionDx-Melanoma classified 76 (35%) tumors as low-risk (class I) and 141 (65%) tumors as high-risk (class II). Within the group of SLN biopsy-negative patients, the 5-year overall survival (OS) rate was 91% in class I patients and 55% in class II patients. Within the group of SLN biopsy-positive patients, the 5-year OS 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.[59,] 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% cutpoints were reported to correspond to 5-year survival in patients with stage IIA and IIB, respectively, although it is unclear whether those cutpoints 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% cutpoint 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 OS is shown in Table 15.

Table 15. Cross-Classification for the DecisionDx-Melanoma and AJCC Tool (79% Cutpoint) 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).[24,]
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 RCTs.

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.[60,61,62,63,64,65,] Given the lack of established clinical validity and no reported long-term outcomes of the test used to select patients for active surveillance, it is not known whether any management changes were clinically appropriate.

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

For the proposed use of the test as a replacement for SLN biopsy (identify patients who are AJCC stage I/II who should receive adjuvant therapy), performance characteristics are also not well-characterized. In addition, 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.

For the proposed use of the test to identify patients who are AJCC stage I/II who should receive enhanced surveillance, there is also a lack of evidence that imaging surveillance or increased frequency of surveillance improves outcomes in stage I/II patients. The National Comprehensive Cancer Network guidelines state that imaging surveillance is not recommended for stage I to IIA and can be 'considered' for IIB to IV but that there is an absence of meaningful data on the association of rigorous routine surveillance imaging with improved long-term outcome for stage IIB to IIC and the recommendations regarding consideration of imaging surveillance remain controversial. While earlier detection of recurrence is thought to be beneficial because lower tumor burden and younger age are associated with improved treatment response and survival, this has not been proven and RCTs are needed to assess whether enhanced surveillance improves survival. The optimal frequency and duration of follow-up surveillance are not standardized and how the surveillance would be altered for DecisionDx class 2 patients has not been defined.

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 to 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.[42,] 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.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Dermatology

In 2019, the American Academy of Dermatology published guidelines of care for the management of primary cutaneous melanoma.[66,] The guidelines state the following regarding gene expression profiling (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 [cutaneous melanoma]. These include comparative genomic hybridization, fluorescence in situ hybridization [FISH], gene expression profiling (GEP), and (potentially) next-generation sequencing."
  - "Ancillary diagnostic molecular techniques (e.g., CGH [comparative genomic hybridization], 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 [American Joint Committee on Cancer] 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 sentinel lymph node (SLN) biopsy or other diagnostic tests for the evaluation of early, thin melanoma because they do not improve survival.[67,] 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-year survival rate.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines (v.2.2023) for cutaneous melanoma made the following statements on use of GEP: [68,]

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:

- "Currently, there is insufficient evidence to support incorporation of current GEP tests into melanoma care. The use of gene expression profiling (GEP) 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 tests to differentiate melanomas at low versus high risk for metastasis should not replace pathologic staging procedures and are not recommended outside of the context of a clinical study or trial. Moreover, since there is a low probability of metastasis in stage I

melanoma and a high proportion of false-positive results using these tests, GEP testing should not guide clinical decision-making in this subgroup. On an individual basis, the likelihood of a positive SLNB may be informed by the use of multivariable nomograms/risk calculators. Ongoing prospective investigation will further inform the use of GEP tests for SLNB risk prediction."

- "Despite commercially available GEP tests being marketed to risk stratify cutaneous melanomas, current GEP platforms do not provide clinically actionable prognostic information when combined or compared with known clinicopathologic factors (e.g., sex, age, primary tumor location, thickness, ulceration, mitotic rate, lymphovascular invasion, microsatellites, and/or SLNB status) or multivariable nomograms/risk calculators. Furthermore, the clinical utility of these tests to inform treatment recommendations and predict patient outcomes has not been established."
- "Various studies of prognostic GEP tests testing suggest its role as an independent predictor of worse outcomes. However, GEP is not superior to Breslow thickness or SLN status and it remains unclear whether available GEP platforms are reliably predictive of outcome across the risk spectrum of melanoma. Validation studies on prospectively collected, independent cohorts (similar to those performed in breast cancer) are necessary to define the clinical utility of molecular prognostic GEP testing as an adjunct to AJCC staging or as part of the multidisciplinary decision-making process to guide 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."

National Society for Cutaneous Medicine

In 2019, the National Society for Cutaneous Medicine published appropriate use criteria for the integration of diagnostic and prognostic GEP assays for management of cutaneous melanoma.[69,] 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 Pigmented Lesion Assay 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 to IIA, SLNBx-) (B= Inconsistent or limited quality patient-oriented evidence)

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

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in April 2023 did not identify any ongoing or unpublished trials that would likely influence this review.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0089U	Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es)
	0090U	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical result (i.e., benign, intermediate, malignant)
	81529	Oncology (cutaneous melanoma), mRNA, gene expression profiling by real-time RT-PCR of 31 genes (28 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk, including likelihood of sentinel lymph node metastasis
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
07/01/2018	BCBSA Medical Policy adoption
02/01/2019	Policy revision without position change
08/01/2019	Policy revision without position change
08/01/2023	Policy reactivated. Previously archived from 07/01/2020 to 07/31/2023

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and

effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Reactivated Policy **Policy Statement:** N/A	**Gene Expression Profiling for Cutaneous Melanoma 2.04.146** **Policy Statement:** I. Gene expression testing, including but not limited to the Pigmented Lesion Assay, in the evaluation of individuals with suspicious pigmented lesions is considered **investigational**. II. Gene expression testing, including but not limited to the myPath Melanoma test, in the evaluation of individuals with melanocytic lesions with indeterminate histopathologic features is considered **investigational**. III. Gene expression testing, including but not limited to DecisionDx-Melanoma, in the evaluation of individuals with cutaneous melanoma is considered **investigational** for all indications.