

Medical Policy



Title: Gene Expression Profiling for Cutaneous Melanoma

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Populations	Interventions	Comparators	Outcomes
Individuals: • With suspicious pigmented lesions (based on ABCDE and/or ugly duckling criteria) being considered for biopsy	Interventions of interest are: • Gene expression profiling with the DermTech Pigmented Lesion Assay to determine which lesions should proceed to biopsy	Comparators of interest are: • Dermatology exam and dermoscopy	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Resource utilization
Individuals: • Who have melanocytic lesions with indeterminate histopathologic features	Interventions of interest are: • Gene expression profiling with the myPath Melanoma test added to histopathology to aid	Comparators of interest are: • Histopathology alone	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity

Populations	Interventions	Comparators	Outcomes
	in diagnosis of melanoma		• Change in disease status • Treatment-related morbidity
Individuals: • With stage I to III cutaneous melanoma	Interventions of interest are: • Gene expression profiling with the DecisionDx-Melanoma test to inform management decisions regarding surveillance	Comparators of interest are: • Sentinel lymph node biopsy • Prognostic tools	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Change in disease status • Resource utilization • Treatment-related morbidity
Individuals: • With stage I or II cutaneous melanoma	Interventions of interest are: • Gene expression profiling with the DecisionDx-Melanoma test to inform management decisions regarding adjuvant therapy	Comparators of interest are: • Sentinel lymph node biopsy • Prognostic tools	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Change in disease status • Resource utilization • Treatment-related morbidity
Individuals: • With stage I or II cutaneous melanoma who are being considered for sentinel lymph node biopsy	Interventions of interest are: • Gene expression profiling with the DecisionDx-Melanoma test to identify patients who can avoid sentinel lymph node biopsy	Comparators of interest are: • Sentinel lymph node biopsy • Prognostic tools	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Change in disease status • Resource utilization • Treatment-related morbidity
Individuals: • Adults with stage I or II cutaneous melanoma, clinically node-negative, who are being considered for sentinel lymph node biopsy	Interventions of interest are: • Clinicopathological and gene expression profiling with the Merlin test to identify patients who can avoid sentinel lymph node biopsy	Comparators of interest are: • Sentinel lymph node biopsy • Prognostic tools	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Change in disease status • Resource utilization • Treatment-related morbidity

DESCRIPTION

Laboratory tests have been developed that detect the expression of different genes in pigmented lesions or melanoma tumor tissue. Test results may help providers and patients decide whether

to biopsy suspicious pigmented lesions, aid in the diagnosis of 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.

OBJECTIVE

The objective of this evidence review is to determine whether gene expression profiling improves the net health outcome in individuals with lesions suspicious for melanoma or with melanoma.

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 2025, close to 105,000 new cases of melanoma are expected to be diagnosed, and more than 8400 people are expected to die of melanoma.²

Risk Factors

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

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

Gene Expression Profiling

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

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. The Pigmented Lesion Assay®, myPath Melanoma®, Merlin™ test (CP-GEP), 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.

POLICY

- A. Gene expression testing, including, but not limited to, the Pigmented Lesion Assay, in the evaluation of individuals with suspicious pigmented lesions is considered **experimental / investigational**.
- B. 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 **experimental / investigational**.
- C. Gene expression testing, including, but not limited to, DecisionDx-Melanoma, in the evaluation of individuals with cutaneous melanoma is considered **experimental / investigational** for all indications.
- D. Gene expression testing, including but not limited to Merlin test, in the evaluation of individuals with cutaneous melanoma is considered **experimental / investigational**.

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.

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.

RATIONALE

This evidence review was created using searches of the PubMed database. The most recent literature update was performed through March 30, 2026.

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

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful.

Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

GENE EXPRESSION PROFILING TO GUIDE INITIAL BIOPSY DECISIONS

Clinical Context and Test Purpose

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 checklist¹¹:

- **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 individual. 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 (ie, 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 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 (OS).

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 (ie, 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 report relevant outcomes²⁴, did not adequately describe the patient characteristics,^{25,26} or did not adequately describe patient selection criteria.^{25,26}

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 (eg, 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.

Van Sambeek et al (2024), Kaufmann et al (2024), and Skelsey et al (2024) evaluated the performance of the Pigmented Lesion Assay test in real-world clinical settings to glean further insight regarding the clinical validity and utility of the test.^{27,28,29} The study characteristics are described in Table 1 and the test performances are reported in Table 2. Overall, the 3 observational studies published similar results for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) as reported in the literature. However, the studies have some major limitations (Table 3 and 4), including but not limited to, clinical context and study population characteristics not adequately described, no comparator used, limited number of follow-up visits, inadequate description of test administration, and no registration of the studies were reported.

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 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	Retrospective Not consecutive or random	Histopathology; consensus diagnosis	Quantitative PCR yielded an amplification curve and a measurable cycle threshold value Either <i>LINC00518</i> or <i>PRAME</i> detected	PLA patch before surgical biopsy; timing between the patch and surgical biopsy unclear	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
	(range, 19 to 97 y)					
Van Sambeek et al (2024) ²⁷ ,	Adults with clinically suspicious lesions for melanoma	Retrospective	Histopathology ; consensus diagnosis	Quantitative PCR yielded an amplification curve and a measurable cycle threshold value Either <i>LINC00518</i> or <i>PRAME</i> detected	Timing of reference or PLA tests is unclear	No blinding
Kaufmann et al (2024) ²⁸ ,	Adults with clinically suspicious lesions for melanoma	Retrospective	Histopathology ; consensus diagnosis	Quantitative PCR yielded an amplification curve and a measurable cycle threshold value Either <i>LINC00518</i> or <i>PRAME</i> detected	Timing of reference or PLA tests is unclear	No blinding
Skelsey et al (2024) ²⁹ ,	Adults with clinically suspicious lesions for melanoma	Retrospective	Histopathology ; consensus diagnosis	Quantitative PCR yielded an amplification curve and a measurable cycle threshold value Either <i>LINC00518</i> or <i>PRAME</i> detected	Timing of reference or PLA tests is unclear	No blinding

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
Van Sambeek et al (2024) ²⁷ ,	893	576	893 tests were used but only 576 were accompanied with at least 1 biopsy or follow-up visit	~6.25%	92 (84 to 100)	79.5 (76.2 to 82.9)	16.9 (11.8 to 24.3)	99.5 (99.1 to 100)
Kaufmann et al (2024) ²⁸ ,	19,653	4461 ^d	Biopsy results and/or	NA	94.2 (91.3 to 96.3)	66.9 (65.5 to 68.4)	20.9 (19.0)	99.2 (98.8)

Study	Initial N	Final N	Excluded Samples	Melanoma Prevalence	Sensitivity ^b	Specificity ^b	PPV ^b	NPV ^b
			follow-up examinations were available for 5,096 lesions with 4461 having ≥ 6 months follow-up				to 22.9)	to 99.5)
Skelsey et al (2024) ^{e 29,}	4282	2197 ^d	Biopsy results and/or follow-up examinations were available for 4282 lesions with 2197 having ≥ 6 months follow-up	NA	97.2 ^c	86 ^c	22.5 ^c	99.9 ^c

NA: not available; 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.

^d Results are for lesions with ≥ 6 months follow-up.

^e Results were combined for Fitzpatrick skin types and confidence intervals were not available.

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	
Van Sambeek et al (2024) ^{27,}	2. Clinical context is unclear 3. Study population characteristics not adequately described		3. No comparison to dermoscopy		1. Follow-up duration not sufficient with respect to natural history of disease

Study	Population^a	Intervention^b	Comparator^c	Outcomes^d	Duration of Follow-Up^e
Kaufmann et al (2024) ²⁸ ,	2. Clinical context is unclear 3. Study population characteristics not adequately described		3. No comparison to dermoscopy		1. Follow-up duration not sufficient with respect to natural history of disease
Skelsey et al (2024) ²⁹ ,	2. Clinical context is unclear 3. Study population characteristics not adequately described		3. No comparison to dermoscopy		1. Follow-up duration not sufficient with respect to natural history of disease

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		
Van Sambeek et al (2024) ^{27,}	2. Not random or consecutive	1. Blinding of histopathology readers not described	1. Patch biopsy administered and timing between procedures not described	1. No registration reported		2. Comparison to other tests not reported.
Kaufmann et al (2024) ^{28,}	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 and timing between procedures not described	1. No registration reported		2. Comparison to other tests not reported.
Skelsey et al (2024) ^{29,}	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 and timing between procedures not described	1. No registration reported		1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not 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 (ie, 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.²⁵ 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 $45 \times 60 \times 2 = 5400$. 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, fluorescence in situ hybridization (FISH), and gene expression profiling (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 individuals 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 Castle Bioscience 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).³⁰

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,^{30,31,32} 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.³³ 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.³⁴

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.^{33,34} In Vergier et al (2011), metastases in the FISH-negative group generally occurred within 5 years.³⁴

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^{30,31,35,36,37,32,38,39} and/or did not adequately describe patient characteristics.³⁰

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.⁴⁰ 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.⁴⁰ 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.⁴¹ 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) ⁴⁰	- 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 (ie, "malignant")	- Final clinical diagnosis established before myPath test - Length of time between biopsy and myPath test unclear	Yes
Clarke et al (2020) ⁴¹	- Melanocytic neoplasms with diagnostic uncertainty - Mean age 63.4 years, 32.7% female (malignant lesions), 42.4 years, 65.1% female (benign lesions)	Retrospective; archived lesions obtained as part of a previous validation study. Case eligibility determined by clinical outcome; otherwise unselected.	Positive: malignant outcome defined as the detection of distant metastasis subsequent to initial biopsy. Lesions known to be malignant at initial biopsy excluded; otherwise no minimum follow-up interval. Negative: benign outcome was defined as absence of local recurrence or metastases throughout a protracted clinical follow-up period (5-year follow-up was not required).	Scores from 0.0 to 11.1 (ie, "likely malignant")	Retrospective testing using archived samples.	Yes

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

Study	Initial N	Final N	Excluded Samples	Melanoma Prevalence	Sensitivity ^a	Specificity ^a	PPV ^a	NPV ^a
Ko et al (2017) ⁴⁰ ,	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) ⁴¹ ,	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) ⁴⁰ ,	4. Study population is not limited to lesions that are indeterminate following histopathology				None noted
Clarke et al (2020) ⁴¹ ,					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) ⁴⁰ ,	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 not reported but were calculated based on data provided. NPV, PPV were not reported
Clarke et al (2020) ⁴¹ ,	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 (ie, 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.

Three decision-impact studies assessed the potential impact of myPath on physicians' treatment decisions in patients with diagnostically challenging lesions.^{42,43,44} 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.⁴⁵ 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.⁴⁶ Nivolumab has been shown to further prolong survival compared with ipilimumab by approximately 35% at 18 months.⁴⁷ 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.⁴⁸

Individuals with stage I and IIA disease should undergo an annual routine physical and dermatologic examination. These individuals typically do not receive surveillance imaging. Individuals 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 individuals classified as stage I to III according to the AJCC criteria. Current guidelines do not recommend adjuvant therapy for AJCC stage I or II individuals 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 individuals.

At least 3 clinical uses for GEP assays have been suggested. One clinical validity study of the DecisionDx-Melanoma test (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."⁴⁹ In another clinical validity study for DecisionDx, the authors concluded that the test's "role in consideration of individuals for adjuvant therapy should be examined prospectively."⁵⁰ 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 individuals at low-risk of being lymph node-positive who can avoid an SLN biopsy (ie, a triage test for SLN biopsy).

The primary clinical use suggested for the CP-GEP Merlin test (SkylineDx) is to identify patients with early-stage cutaneous melanoma who are at low risk of sentinel lymph node (SLN) metastasis and may safely forgo SLN biopsy. In the largest prospective clinical validity study of the CP-GEP test (described below), the authors concluded that a low-risk result "places an individual patient in the 5% to 10% risk category" for SLN positivity and that the test "may add value for shared patient-surgeon decision-making," particularly when "a 10% threshold is clinically appropriate, such as in older patients or those with comorbidities."⁵¹ In a retrospective clinical validity study, the authors concluded that CP-GEP "can risk stratify patients with early-stage melanoma based on recurrence risk" and may support "identification of patients at high risk for recurrence and death" to guide decisions about "SLNB referral, adjuvant therapy access, and surveillance intensity."⁵² This use of the test would be as a triage tool 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 the Merlin test to guide decisions regarding:

1. Provide a "personalized estimate of metastatic risk, supporting clinical decisions such as whether to perform SLNB."
2. Deliver "individualized risk estimates for melanoma recurrence and survival over 5 to 10 years, helping guide long-term management and follow-up care."

The use of the test reviewed is to select individuals with cutaneous melanoma at low-risk of being lymph node-positive who can avoid an SLN biopsy (ie, 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 (Castle Biosciences) 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

DecisionDx Test

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).⁴⁹ 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 DecisionDx-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."

Merlin Test

The test being considered is the SkylineDx clinicopathologic and gene expression profiling (CP-GEP) Merlin test. The assay is a gene expression profile test that combines expression analysis of 8 genes (*MLANA*, *GDF15*, *CXCL8*, *LOXL4*, *TGFBR1*, *ITGB3*, *PLAT*, *SERPINE2*) from formalin-fixed, paraffin-embedded primary tumor tissue with 2 clinicopathologic factors, patient age and Breslow thickness, to generate a binary low-risk or high-risk classification for sentinel lymph node (SLN)

metastasis. The test is available as a laboratory-developed test from SkylineDx's CAP/CLIA-certified laboratory in San Diego, California.

The development of the test was described in Bellomo et al (2020).⁵³ To develop the CP-GEP model, the authors analyzed a discovery cohort of 754 consecutive T1 to T3 primary cutaneous melanomas from the Mayo Clinic who underwent SLN biopsy within 90 days of diagnosis. Investigators used logistic regression to combine gene expression data from 8 genes associated with melanoma metastasis with patient age and Breslow thickness into a single integrated algorithm. The 8 genes were selected based on their association with melanoma tumor biology and metastatic potential. The reference standard was SLN biopsy pathology (positive or negative). The model was designed to predict a binary SLN outcome at diagnosis rather than long-term recurrence, and no minimum clinical follow-up period was required for inclusion. Information about treatments received was not provided in the development study.

The Merlin test report provides a binary classification of low-risk or high-risk. According to the manufacturer's website, the test result "is determined by analyzing the expression of 8 genes from the patient's tumor sample, combined with patient age and tumor thickness." The report also provides a personalized estimate of metastatic risk and individualized risk estimates for melanoma recurrence and survival over 5 to 10 years.

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.⁵⁴

Online tools are available to predict prognosis based on the AJCC guidelines. The original AJCC tool was developed by Soong et al (n.d.).⁵⁵ Callender et al (2012) incorporated SLN biopsy results into a revised tool (<http://www.melanomacalculator.com/>).⁵⁶

Outcomes

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

If the test is used to 'rule-in' a higher risk for recurrence or metastasis in AJCC stage I or IIA individuals, a negative DecisionDx (class 1) test result would not change outcomes. Per guidelines, the individuals would not receive adjuvant therapy or enhanced surveillance, just as without the DecisionDx test. A positive DecisionDx (class 2) test result would indicate that an individual 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 individuals who would benefit from enhanced surveillance in AJCC stage IIB to III individuals:

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 an individuals 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 individuals , a negative DecisionDx (class 1) test result would indicate that an individuals 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 individuals who can avoid SLN biopsy:

For individuals meeting guideline-recommended criteria for SLN biopsy, a positive DecisionDx (class 2) test result would not change outcomes. The individuals 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 individuals 55 years of age and older who have tumors less than 2 mm thick (T1 to T2) would indicate that an individuals 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 individuals that would be eligible for beneficial adjuvant treatment and potentially reduced survival.

For individuals meeting guideline-recommended criteria for SLN biopsy, a high-risk Merlin test result would not change outcomes. The individuals would proceed to SLN biopsy, as they would have without the test, and treatment and imaging decisions would depend on SLN biopsy results. A low-risk test result in individuals with T1 to T3 cutaneous melanoma would indicate that an individual's risk of SLN metastasis is in the 5% to 10% range and that the individual could be a candidate to avoid SLN biopsy through shared decision-making with the treating surgeon. 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 individuals that would be eligible for beneficial adjuvant treatment and potentially reduced survival. In the MERLIN_001 prospective study, 7.1% of patients classified as low-risk via the Merlin assay and were SLN positive, indicating that approximately 1 in 14 low-risk patients would have undetected nodal disease if SLN biopsy were deferred on the basis of the test result.

The risk of recurrence decreases over time but does not reach 0. In a study of 1568 individuals with stage I melanoma, Dicker et al (1999) found that 80% of the recurrences occurred within the first 3 years.⁵⁷ A prospective study by Garbe et al (2003) reported that, for stage I and II individuals, the risk of recurrence was low after 4.4 years.⁵⁸ Among 4731 individuals treated for more than 10 years at 1 institution, Faries et al (2013) found the majority of recurrences occurred in the first 5 years.⁵⁹ However, 7% of individuals experienced recurrence after 10 years (median, 16 years). Even among stage I/II individuals, recurrence after 10 years occurred in 2% of individuals. 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).

DECISIONDX

REVIEW OF EVIDENCE

Systematic Review and Meta-Analysis

Durham et al (2024) collected data from 13 studies, comprising of 14,760 individuals, and conducted a meta-analysis to provide a comprehensive assessment of the current evidence of DecisionDx test's prognostic performance.⁶⁰ Critical appraisal of these studies using the Begg's test and Egger's regression test indicated an overall low risk of bias with the potential sources of bias attributed to study confounding, attrition, and participation. Relevant survival outcomes, based on the natural history of melanoma, for the GEP classes denoted by DecisionDx testing are displayed in Table 9 using a random effects estimates model to account for the confounding heterogeneity and variability of the studies used. The 5-year melanoma-specific survival (MSS) rate for the overall population was 97.5% (95% CI: 86.5 to 99.6). Additional survival-related outcomes (3-year overall survival, 3-year recurrence-free survival, 3-year distant metastasis-free survival, and 5-year MSS) were assessed and demonstrated better outcomes for Class 1 and 1A compared to Class 2 and 2B. Although this meta-analysis provide a consensus of the current literature for relevant survival outcomes of interest there are still some notable limitations of this review, including but not limited to, a small number of studies available for GEP class per outcome, heterogeneity among studies, lack of information on study treatments used during the studies, and the GEP test's categorization conflicts with the Melanoma Prevention Working Group's recommendations for GEP tests to be reported as continuous variables. Further evidence via randomized-control trials evaluating long-term outcomes of patients with GEP-informed testing is necessary to further define the possible role of the DecisionDx test in the management of patients with melanoma.

Table 9. Summary of Random Effects Estimates for Survival-Related Outcomes in Durgham et al (2024)⁶⁰,

Outcome	Number of Studies	Patients (N)	Random Effects Estimate (95% CI)	I ² (%)
Class IA 5-year Recurrence-free survival %	3	2085	95.0 (91.8 to 97.0)	91.6
Class IB 5-year Recurrence-free survival %	2	1647	83.3 (74.4 to 89.5)	96.8
Class IIA 5-year Recurrence-free survival %	2	1647	82.3 (65.6 to 91.9)	98.9
Class IIB 5-year Recurrence-free survival %	3	2085	50.5 (42.4 to 58.7)	93.4
Class IA 5-year Distant Met-free survival %	3	2085	98.0 (96.1 to 98.9)	81.5
Class IB 5-year Distant Met-free survival %	2	1647	87.1 (79.8–92.1)	96.1
Class IIA 5-year Distant Met-free survival %	2	1647	86.8 (72.2 to 94.4)	98.7
Class IIB 5-year Distant Met-free survival %	3	2085	62.4 (52.5 to 71.4)	95.5

The 31-GEP test classifies melanoma tumors into 4 risk classes: Class 1A (lowest risk), Class 1B and 2A (intermediate risk), and Class 2B (highest risk).

CI: confidence interval; I²: heterogeneity

Observational Studies

Several papers were excluded from the evaluation of clinical validity. Hsueh et al (2017), Podlipnik et al (2019), Hsueh et al (2021), Kriza et al (2024), Guenther et al (2025), and Bailey et al (2023) 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, 3.2 years, and 18 months, respectively).^{61,62,63,64,65} Samples used in Gerami et al (2015)⁴⁹, and Ferris et al (2017)²⁵, 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.^{66,67,49,50} 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.⁶⁸ Marks et al (2019) describes the development of a cutpoint.⁶⁹

Four independent clinical validity studies meeting eligibility criteria have been conducted. Characteristics and results are summarized in Tables 10 and 11 and briefly in the paragraphs that follow.

Table 10. 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) ⁴⁹ ; 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) ⁵⁰	- 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) ⁷⁰	- Patients who were treated for primary invasive CM of any Breslow depth within 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	Retrospective Consecutive	5-y MFS	Commercial test cutoffs used	Institution offered DecisionDx testing to newly diagnosed and those treated within the previous 5 years	Yes
Keller et al (2019) ⁷¹	Patients had CM (91% stage I/II), opted for GEP testing	Prospective	3-yr RFS (5-y RFS reported in	Commercial test cutoffs used	Patients diagnosed between	Yes

Study	Study Population	Design	Reference Standard / Outcome Measure	Threshold Score for Positive DecisionDx Test	Timing of Reference and DecisionDx Tests	Blinding of Assessors
	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		a figure only)		2013 and 2015 GEP reported to be performed concurrently with SLN biopsy	

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

Table 11. 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) ⁴⁹ ; 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) ⁵⁰		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) ⁷⁰ ,	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) ⁷¹ ,	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).⁴⁹ 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 11 based on data provided. Reclassification of patients in AJCC stages to DecisionDx classes is shown in Table 12.

Table 12. Reclassification of Patients Based on AJCC Stages to DecisionDx Classes in the Gerami Validation Cohort

AJCC Stage	DecisionDx Class		
	<i>Class 1 (Low-Risk), N (row %)</i>	<i>Class 2 (High-Risk), N (row %)</i>	<i>Total</i>
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	

AJCC Stage	DecisionDx Class		
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).⁴⁹

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.⁵⁰ 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. The 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 SLN 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 12. The reclassification of patients based on SLN biopsy status using DecisionDx classes is shown in Table 13. 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 14 and 15.

Table 13. 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).⁵⁰

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.⁷⁰ Study characteristics and results were reported in the preceding Tables 10 and 11. 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.⁷¹ Study characteristics and results were reported in the preceding Tables 10 and 11. 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 14. 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) ⁴⁹ ; 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) ⁵⁰ .	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) ⁷⁰ .			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) ⁷¹ .				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 15. 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) ⁴⁹ ; 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) ⁵⁰	2. Not consecutive or random		1. Time between collection of biopsy and DecisionDx not described	1. No registration reported	1. No description of number of samples (if any) that failed to produce results or were indeterminate	
Greenhaw et al (2018) ⁷⁰			1. Some samples collected after treatment	1. No registration reported		
Keller et al (2019) ⁷¹				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 (ie, 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.⁷² 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)⁴⁹, 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 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.⁷³ 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 16.

Pazhava et al (2024) retrospectively analyzed electronic health records from patients with cutaneous melanoma who underwent GEP testing to evaluate the current clinical utility and performance of the DecisionDx test.⁷⁴ The study examined the prognostic performance of the GEP classifications using 2 survival outcomes: relapse-free survival (RFS) and melanoma-specific survival (MSS). The median follow-up for all survival endpoints was 38.7 months (~ 3 years), albeit there was significant variability in follow-up durations. Clinical utilization was assessed by determining if the GEP test influenced management decisions regarding a patient's melanoma diagnosis. Overall, the GEP classification only affected 18.5% of patients' management decisions with 2 cases forgoing SNL biopsy, 3 cases referred to medical oncology, and 5 cases that had adjusted postdiagnosis surveillance, but ultimately these classifications did not significantly alter treatment decisions or led to better net health outcomes. Kaplan-Meier analysis indicated that survival curves for RFS and MSS between Class 1 versus Class 2 patients were not statistically different (RFS: HR = 1.12, p=.84, MSS: HR = 0.64, p=.76). However, patients with a positive SNL biopsy had worse RFS (50.0%, 95% CI [5.8 to 84.5]; 60.0%, 95% CI [36.6–77.2], respectively) and MSS (75.0%, 95% CI [12.8 to 96.1] 93.8%, 95% CI [63.2 to 99.1], respectively) rates compared to SNL biopsy negative patients, albeit not statistically significant.

Table 16. 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).²⁵

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.^{75,76,77,78,79,80,74} 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.

MERLIN TEST

REVIEW OF EVIDENCE

Systematic Review and Meta-Analysis

Wong et al (2025) conducted a PROSPERO-registered systematic review and meta-analysis of 4 independent external validation studies of the CP-GEP model published between 2020 and June 2024 (See Table 17).⁸¹ The pooled analysis included 1,061 individuals with a pooled median age of 60 years, median Breslow thickness of 1.55 mm, and overall sentinel lymph node biopsy (SLNB) positivity rate of 17.8%. Quality assessment using the QUADAS-2 tool identified no studies at high risk of bias. Across all primary tumor categories (pT1 to pT4), pooled sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and SLNB reduction rates are presented in Table 17. The model performed best for pT2 melanomas (n=483; SLNB positivity 14.3%), with pooled sensitivity of 91% (95% confidence interval [CI], 82% to 96%), specificity of 35% (95% CI, 30% to 39%), NPV of 96% (95% CI, 91% to 98%), and SLNB reduction rate of 31% (95% CI, 27% to 35%). For pT3 melanomas, the SLNB reduction rate was only 3% (95% CI, 1% to 6%), indicating minimal utility in this subgroup. For pT1 melanomas, high SLNB reduction rate was observed (72%; 95% CI, 55% to 85%) but with wide confidence intervals and substantial heterogeneity, reflecting limited sample size and low SLNB positivity (6.8%). The authors concluded that the CP-GEP model can reduce the number of unnecessary SLNBs performed, particularly in pT2 patients. Notable limitations include, but are not limited to, limited number of studies; blinding between the index test and reference standard not described in 2 of the studies; substantial heterogeneity in overall (pT1–pT4) pooled estimates for specificity, PPV, and SLNB reduction rate, with insufficient numbers of pT1 and pT4 studies to support reliable subgroup inference; and the absence of individual patient data.

Table 17. Summary of Results CP-GEP Study (Test Performance)^a

Study	Prevalence / Risk Group Distribution	Sensitivity (95% CI)	Specificity (95% CI)	PPV ^c (95% CI)	NPV ^c (95% CI)	SLNB RR ^b (95% CI)
Pooled Overall (pT1–pT4; N=1061)	SLNB+ rate: 17.8% (189/1,061)	93% (95% CI, 88% to 96%); I ² =0%	32% (95% CI, 23% to 41%); I ² =87.3%	24% (95% CI, 18% to 31%); I ² =76.9%	95% (95% CI, 92% to 97%); I ² =0%	SLNB RR: 27% (95% CI, 20% to 35%); I ² =87.3%
pT2 subgroup (n=483, 45%)	SLNB+ rate: 14.3%	91% (95% CI, 82% to 96%); I ² =0%	35% (95% CI, 30% to 39%); I ² =0%	20% (95% CI, 14% to 27%); I ² =50.4%	96% (95% CI, 91% to 98%); I ² =0%	SLNB RR: 31% (95% CI, 27% to 35%); I ² =0%
pT1 subgroup (n=177, 17%)	SLNB+ rate: 6.8%	22% (95% CI, 1% to 93%); I ² =59.7%	72% (95% CI, 56% to 84%); I ² =70.9%	4% (95% CI, 0% to 58%); I ² =56.4%	94% (95% CI, 89% to 97%); I ² =0%	SLNB RR: 72% (95% CI, 55% to 85%)
pT3 subgroup (n=272, 26%)	SLNB+ rate: 27.2%	99% (95% CI, 91% to 100%); I ² =0%	4% (95% CI, 2% to 8%); I ² =20.4%	29% (95% CI, 19% to 43%); I ² =76.5%	87% (95% CI, 46% to 98%); I ² =0%	SLNB RR: 3% (95% CI, 1% to 6%)

Adapted from ⁸¹.CI: confidence interval; I²: inconsistency index; SLNB: sentinel lymph node biopsy; SLNB RR: sentinel lymph node biopsy reduction rate

^a Substantial heterogeneity (I² >75%) was observed for the overall pooled (pT1–pT4) specificity (I²=87.3%), PPV (I²=76.9%), and SLNB RR (I²=87.3%). No substantial heterogeneity was observed for the pT2 subgroup for any metric (I²=0% for sensitivity, specificity, NPV, and SLNB RR), making pT2 estimates the most stable and clinically interpretable pooled results. I² >75% represents substantial heterogeneity per the pre-specified threshold.

^b SLNB reduction rate (SLNB RR) = ([TN+FN]/[TP+TN+FP+FN]): proportion of patients classified CP-GEP low-risk who could forgo SLNB.

Nonrandomized Clinical Studies

Key study characteristics and results are presented in Table 18 and 19.

Four independent external validation studies of the Merlin CP-GEP model were published between 2020 and June 2024 and covered in the systematic review and meta-analysis by Wong et al (2025). ^{82, 83, 84, 85} Mulder et al (2021) reported a model that had an AUC of 0.66 (95% CI, 0.59 to 0.74) with 20% of the individuals (42/210) classifying as low risk; among these, 4 (9.5%) had a positive SLN. Yousaf et al (2021) evaluated the CP-GEP model in a pre-planned subgroup analysis of patients 65 years or older (n=77) and reported a SLNB reduction rate of 43.1% (95% CI, 29.3% to 57.8%) at an NPV of 95.5% (95% CI, 77.2% to 99.9%) in the T1–T2 population, suggesting CP-GEP may provide particular value in older patients for whom SLNB is often elective. Johansson et al (2022) validated the CP-GEP model in 421 consecutive patients and compared it with the MSKCC and MIA nomograms in the pT1–T2 subpopulation (n=358), CP-GEP achieved a higher SLNB reduction rate (34.2% vs. 25.2% MSKCC vs. 0.5% MIA) with comparable NPV (95.7% vs. 96.1% MSKCC vs. 100% MIA). In patients 65 years or older (n=171), the pT1–T3 NPV was 97.6% (95% CI, 87.1% to 99.9%) with a sentinel lymph node biopsy (SLNB)

reduction rate of 29.5% (95% CI, 22.1% to 37.8%). Stassen et al (2023) conducted the first prospective multicenter evaluation of the CP-GEP model in a clinical implementation context, evaluating 222 individuals who underwent SNLB with T1b–T4 primary cutaneous melanoma. Additionally, 3 more retrospective validation studies were published in 2025 and the test performance characteristics from these validation studies are denoted in Table 18 with their study characteristics reported in Table 19, respectively. ^{86,87,88} Zijlker et al (2025) reported the CP-GEP assay classified 68 individuals (28%) as low risk and 175 (72%) as high risk, while performing the best in the pT1b–pT2a subgroup (n=132), with an NPV of 93.3% (95% CI 83.8 to 98.2%) and an SLNB reduction rate of 45.5% (95% CI 36.8 to 54.3%). For 5-year prognostic outcomes, CP-GEP low-risk patients had recurrence-free survival (RFS) of 89.6% (95% CI 79.5 to 94.9%) versus 76.8% (95% CI 69.8 to 82.4%) for high-risk patients (HR: 2.41), distant metastasis-free survival (DMFS) of 95.6% (95% CI 86.9 to 98.5) versus 81.3% (95% CI 74.5 to 86.4; HR: 4.46), and melanoma-specific survival (MSS) of 98.5% (95% CI 89.9 to 99.8) versus 88.9% (95% CI 83.2 to 92.8; HR: 7.88). Weitemeyer et al (2025) reported results from a retrospective multicenter cohort (n=536) validation study of the CP-GEP (Merlin Assay) and in a secondary analysis using a 0.3 mm SLN tumor burden cutoff to reclassify clinically irrelevant nodal disease, the overall NPV improved to 95.4% (95% CI 91.8 to 97.8%) and T1 NPV to 98.4% (95% CI 94.5 to 99.8%) suggesting that lowering the tumor burden threshold can improve the test performance without compromising the risk of SLN metastasis. Additionally, the CP-GEP model was compared to the MIA nomogram (n=507 evaluable) and classified 42.4% of individuals as low risk (NPV 91.2%) versus 8.1% by MIA (NPV 95.1%). Pazhava et al (2025) evaluated CP-GEP performance specifically in 250 individuals with primary cutaneous melanoma of the head and neck region. In T1–T2 melanomas (n=167), the SLNB reduction rate was 56.3% (95% CI, 48.4% to 63.9%) at an NPV of 98.9% (95% CI, 94.2% to 100%). Among 215 SLNB-negative patients, the CP-GEP assay further stratified outcomes for low-risk patients (n=100) with a 5-year RFS of 86.1% compared to 68.1% in high-risk patients (hazard ratio [HR] 2.49; p<.05), 5-year DMFS of 92.7% vs. 75.8% (HR: 3.15; p<.05), and 5-year MSS of 95.3% vs. 85.5% (HR: 2.26; p=.175).

Amaral et al (2025) evaluated CP-GEP for risk stratification in 930 individuals with clinical stage I/II primary cutaneous melanoma from the University of Tuebingen, Germany, who did not undergo SLNB, with a median follow-up of 165 months. ⁵² The CP-GEP assays classified 879 individuals (94.5%) as low risk and 51 (5.5%) as high risk. Low-risk patients had significantly better 10-year RFS (94.5% vs. 37.5%; hazard ratio [HR], 20.07; p<.001), 10-years DMFS (98% vs. 70%; HR: 19.44; p<.001), MSS (98.6% vs. 66.8%; HR: 35.85; p<.001), and OS (80.2% vs. 38.4%; HR: 5.59; p<.001) compared with high-risk patients. Limitations include the retrospective single-center design conducted at a German institution with a predominantly Caucasian European population, predominantly thin melanoma (median Breslow thickness 0.50 mm overall; 76.8% T1a), and marked Breslow thickness differences between risk groups (median 0.50 mm for Low Risk vs. 3.60 mm for High Risk), which may substantially drive survival differences independent of the genomic component. No SLNB data were available, and no actionable treatment pathway currently exists for stage I-IIA patients identified as high-risk by CP-GEP.

Hieken et al (2025) reported results of the MERLIN_001 study, the largest prospective, multicenter, double-blinded evaluation of the CP-GEP test for SLN metastasis risk stratification. ⁵¹ Nine U.S. academic medical centers enrolled 1,761 eligible individuals with T1 to T3 cutaneous melanoma and clinically negative regional lymph nodes who elected for SLNB. The Merlin assay classified 651 individuals (37.0%) as low risk and 1,110 (63.0%) as high risk.

Among low-risk cases, 46 (7.1%) were SLN positive, yielding an NPV of 92.9% (95% CI, 90.7% to 94.8%). Among high-risk cases, 264 (23.8%; 95% CI, 21.3% to 26.4%) were SLN positive, a 3.4-fold higher risk. The percentage of cases classified as low risk declined with increasing T category (T1: 68.2%; T2: 32.9%; T3: 2.8%), indicating limited utility in T3 tumors. In the largest subset, patients with clinical stage IB melanoma (n=1,187; 67.4% of the study population), 49.3% were classified as low risk with an observed SLN-positive rate of 6.5% (95% CI, 4.6% to 8.8%) compared with 18.3% (95% CI, 15.3% to 21.6%) in high-risk cases. The primary study objective, with an upper bound of the 95% CI for SLN positivity in low-risk cases, was not met as a majority of patients had a >6% risk of sentinel node metastasis. In patients 65 years or older (n=832; 47.2%), 42.1% were classified as low risk with an SLN-positive rate of 6.6% (95% CI, 4.2% to 9.7%) compared with 20.3% (95% CI, 16.8% to 24.2%) in high-risk cases. Results were consistent across anatomic sites, histologic subtypes, and mitotic count categories. Notable limitations include surgeon-selected enrollment, absence of centralized pathology review, absence of race/ethnicity data, and the absence of health outcome data in the current publication. The test was not recommended to replace SLNB but to inform shared decision-making.

Table 18. Clinical Validity Study Characteristics of the Merlin Test for SLNB

Study	Study Population	Design	Reference Standard / Outcome Measure	Threshold Score for Positive Merlin Test ^a	Timing of Reference and Merlin Tests	Blinding of Assessors
Mulder et al (2021) ⁸²	Adults, median Breslow 2.05 mm, T2 (45%) and T3 (33%) predominant, SLN+ 27% (56/210)	Retrospective, single-center	SLN pathology per EORTC Rotterdam tumor load / Dewar topography criteria. Minimal tumor burden (≤ 0.4 mm subcapsular or ≤ 0.1 mm any location) counted as positive.	Predefined cut-off probability 0.063 from development cohort. Binary: low risk / high risk.	All eligible consecutive patients 2007 to 2017 linked to nationwide PALGA pathology registry. FFPE retrieved from any NL center.	FFPE shipped blinded to SkylineDx; SLNB status not disclosed to SkylineDx during analysis.
Yousaf et al (2021) ⁸³	Adults, median Breslow 1.30 mm, T1b (34%) and T2a (31%) predominant, SLN+ 21% (44/208)	Retrospective, two-center U.S.	SLN pathology per institutional protocols.	Predefined cut-off 0.063 from development cohort. Binary: low risk / high risk. Same threshold as Mulder 2021.	SLNB within 90 days of primary diagnosis. Mayo Clinic (MN, AZ, FL; 2004–2019) + West Virginia University (2007 to 2014). Blinding between SLNB and CP-GEP results not explicitly described.	No

Study	Study Population	Design	Reference Standard / Outcome Measure	Threshold Score for Positive Merlin Test ^a	Timing of Reference and Merlin Tests	Blinding of Assessors
Johansson et al (2022) ⁸⁴ ,	Adults, median Breslow 1.8 mm, T2 (50%) and T3 (28%) predominant, SLN+ 13% (54/421)	Retrospective, population-based single-center consecutive cohort.	SLN pathology per AJCC 8th edition criteria.	Predefined cut-off 0.063. Binary: low Risk / high Risk. Same threshold as development cohort.	All 489 SLNB patients 2006–2014 assessed (Sahlgrenska University Hospital, Gothenburg, Sweden;); 421 included after exclusions. Board-certified dermatopathologist reviewed and restaged all tumors	FFPE coded and shipped blinded to SkylineDx for qPCR. All samples blinded regarding SLNB outcome.
Stassen et al (2023) ⁸⁵ ,	Adults, median Breslow 1.4 mm, SLN+ 15.7% (35/222 who underwent SLNB).	Prospective, multicenter. All eligible T1b–T4 patients enrolled.	SLN pathology per EORTC Melanoma Group pathology protocol; SN mapping and SLNB performed same day.	Predefined cut-off 0.063. Binary: low Risk / high Risk. Same threshold as development cohort.	FFPE centrally revised at Erasmus MC before coded shipment to SkylineDx (July 2020 to August 2022.).	CP-GEP results blinded during analysis.
Pazhava et al (2025) ⁸⁸ ,	Adults, median Breslow 1.6 mm, and SLN+ 14% (35/250)	Retrospective; data from archived samples. SLNB data prospectively collected	SLN pathology per institutional guidelines; each site followed own protocols.	Published Bellomo 2020 algorithm thresholds. Binary: low risk / high risk. FFPE blocks (50 microns) from dermatopathology archives.	SLNB within 90 days of diagnosis (Mayo Clinic (2004–2021 & University Hospitals Cleveland Medical Center 2007–2017)	SLNB status blinded for SkylineDx laboratory personnel during CP-GEP analysis.
Amaral et al (2025) ⁵² ,	Stage I/II cutaneous melanoma, adult, median Breslow 0.50 mm; 91% stage IA.	Retrospective single-center cohort; FFPE from Central Malignant Melanoma Registry	SLN pathology per institutional guidelines; long-term clinical outcomes: RFS (primary), DMFS, MSS, OS via Kaplan-Meier and Cox regression. Cause of death linked to German public health registries.	Same algorithm and binary output as all other studies. Low risk / high risk.	Retrospective; University of Tuebingen, Germany; 2000–2020.	No blinding possible.

Study	Study Population	Design	Reference Standard / Outcome Measure	Threshold Score for Positive Merlin Test ^a	Timing of Reference and Merlin Tests	Blinding of Assessors
Zijlker et al (2025) ⁸⁶ ,	Stage I/II cutaneous melanoma, adult, median Breslow 1.80 mm; SLN+ 21.8% (53/243)	Nonconcurrent prospective; biobank	SLN pathology per AJCC 8th edition criteria/SLN metastasis; 5-yr RFS, DMFS, MSS	Binary: CP-GEP low/high risk	Diagnosis between 2007–2015 at Netherlands Cancer Institute; Follow-up cutoff Jan. 2022; median 91 months	No blinding
Weitemeyer et al (2025) ⁸⁷ ,	Stage I to III cutaneous melanoma, adult, median Breslow 1.3mm; SLNB+ 18.1% (97/536)	Retrospective multicenter; Danish Melanoma Database	SLN pathology per AJCC 7th edition criteria/SLN metastasis only (no survival outcomes)	Binary: CP-GEP low/high risk (cutoff 0.063); 0.3mm SLN burden secondary analysis	Diagnosis between 2010 to 2015; CP-GEP Oct. 2020 to Dec. 2021	SLNB status blinded for SkylineDx laboratory personnel during CP-GEP analysis.
Hieken et al (2025) ⁵¹ ,	Adults, median Breslow 1.30 mm, T1 to T3 cutaneous melanoma, SLN+ 17.6% (310/1761)	Prospective, multicenter, double-blinded prognostic study.	SLN pathology: any malignant cells including isolated tumor cells = positive; institutional protocols; no centralized pathology review.	Predefined cut-off from Bellomo 2020. Binary: low risk / high risk.	FFPE tissue from the primary tumor biopsy was requested, and if available, submitted in deidentified fashion to SkylineDx.	Double-blinded: patients and surgeons blinded to CP-GEP results throughout study.

EORTC: European Organization for Research and Treatment of Cancer; CP-GEP: clinicopathologic gene expression profile; FFPE: formalin-fixed paraffin-embedded; LVI: lymphovascular invasion; PALGA: nationwide Dutch histopathology/cytopathology registry; qPCR: quantitative polymerase chain reaction; SLNB: sentinel lymph node biopsy; SR/MA: systematic review and meta-analysis.

^aAll studies use the published Bellomo 2020 algorithm with predefined cut-off probability of 0.063 for binary Low Risk / High Risk classification. Mulder 2021 used a bridged threshold for the QuantstudioDx platform.

Table 19. Clinical Validity Study Results of the Merlin Test for SLNB

Study	N	Excluded Samples	Prevalence / Risk Group Distribution	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Mulder et al (2021) ^{82,}	210 (pT1-T3, n=175)	123 excluded (no/insufficient FFPE n=85; QC failure n=2; T4 excluded from primary analysis). Platform bridging required.	SLNB+: 27% (56/210) Low risk: 20% (42/210) High risk: 80% (168/210)	pT1–pT3: 91.5% (80.1 to 96.6)	pT1–pT3: 29.7% (22.5 to 38.1)	pT1–pT3: 32.3% (25.0 to 40.7)	pT1–pT3: 90.5% (77.9 to 96.2)
Yousaf et al (2021) ^{83,}	208 (pT1-T2, n=153; pT1-T3, n=193)	Per exclusion criteria: prior melanoma, >90-day SLNB, M1, insufficient tissue, missing data, inadequate RNA.	SLNB+: 21% (44/208) Low risk: 31.2% (65/208) High risk: 68.8% (143/208)	pT1–T2: 45.7% (30.9 to 61.0) pT1–T3: 38.6% (26.0 to 52.4)	pT1–T2: 80.0% (28.4 to 99.5) pT1–T3: 92.3% (64.0 to 99.8)	pT1–T2: 13.8% (3.9 to 31.7) pT1–T3: 25.5% (13.9 to 40.3)	pT1–T2: 95.5% (77.2 to 99.9) pT1–T3: 95.7% (78.1 to 99.9)
Johansson et al (2022) ^{84,}	421 (pT1-T2, n=202; pT1-T3, n=303)	68 excluded (consent n=1, CJD n=1, FFPE unavailable n=42, insufficient FFPE n=12, incorrect Dx n=4, duplicate n=2, SLNB failed n=2; QC failure n=4). Head/neck excluded.	SLNB+: 13% (54/421) Low risk: 20% (86/421) High risk: 80% (335/421)	pT1–T2: 83.3% (58.6 to 96.4) pT1–T3: 90.3% (74.2 to 98)	pT1–T2: 35.9% (28.9 to 43.3) pT1–T3: 24.6% (19.6 to 30.2)	pT1–T2: 11.3% (6.5 to 17.9) pT1–T3: 12% (8.1 to 16.9)	pT1–T2: 95.7% (87.8 to 99.1) pT1–T3: 95.7% (88 to 99.1)
Stassen et al (2023) ^{85,}	222	19 excluded post-enrollment (missing data). 38 did not undergo SLNB (patient preference n=18; parotid SN n=11; SN not identified n=9).	SLNB+: 15.7% (35/222) Low risk: 38.5% (100/260)	pT1–T4: 91.4% (76.9 to 98.2)	pT1–T4: 45.8% (38.6 to 53.2)	pT1–T4: 23.7% (16.8 to 31.8)	pT1–T4: 96.7% (90.6 to 99.3)

Study	N	Excluded Samples	Prevalence / Risk Group Distribution	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
			High risk: 61.5% (160/260)				
Pazhava et al (2025) ^{88,}	250	1,033 excluded (non-head/neck n=963; QC failure n=27; clinical criteria n=35; duplicate n=6; no material n=2).	SLNB+: 14% (35/250) Low risk: 40.8% (102/250) High risk: 59.2% (148/250)	pT1–T2: 92.9% (66.1 to 99.8) pT1–T3: 93.5% (78.6 to 99.2) pT1–T4: 94.3% (80.8 to 99.3)	pT1–T2: 60.8% (66.1 to 99.8) pT1–T3: 48.5% (41.5 to 55.6) pT1–T4: 46.5% (39.7 to 53.4)	pT1–T2: 17.8% (9.8 to 28.5) pT1–T3: 21.6% (15 to 29.6) pT1–T4: 22.3% (15.9 to 29.9)	pT1–T2: 98.9 (94.2 to 100) pT1–T3: 98% (93 to 99.8) pT1–T4: 98% (93.1 to 99.8)
Amaral et al (2025) ^{52,}	930	63 excluded (61 QC failures; 2 clinical criteria).	No SLNB performed (survival study) Low risk: 94.5% (879/930) High risk: 5.5% (51/930)	NR	NR	NR	NR
Zijlker et al (2025) ^{86,}	243	9 excluded	SLNB+: 21.8% (53/243) Low risk: 28.0% (68/243) High risk: 72.0% (175/243)	pT1–pT4: 92.5% (81.8 to 97.9) pT1b–pT2a: 80.0% (56.3 to 94.3)	pT1–pT4: 33.7% (27.0 to 40.9) pT1b–pT2a: 50.0% (40.4 to 59.6)	pT1–pT4: 28.0% (21.5 to 35.3) pT1b–pT2a: 22.2% (13.3 to 33.3)	pT1–pT4: 94.1% (85.6 to 98.4) pT1b–pT2a: 93.3% (83.8 to 98.8)

Study	N	Excluded Samples	Prevalence / Risk Group Distribution	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
						to 33.6)	to 98.2)
Weitemeyer et al (2025) ^{87,}	536	697 excluded (QC failure n=7; screen failures n=690)	SLNB+: 18.1% (97/536) Low risk: 40.9% (219/536) High risk: 59.9% (317/536)	pT1–pT3: 80.4% (71.1 to 87.8)	pT1–pT3: 45.6% (40.8 to 50.4)	pT1–pT3: 24.6% (20.0 to 29.7)	pT1–pT3: 91.3% (86.8 to 94.7)
Hieken et al (2025) ^{51,}	1761	380 excluded (screen failures n=91; no/unsuccesful SLNB n=86; consent withdrawal n=4; qPCR failure n=26; RNA QC failure n=15; no FFPE available n=158).	SLNB+ 17.6% (310/1,761) Low risk: 37.0% (651/1,761) High risk: 63.0% (1,110/1,761)	NR	NR	NR	NR

CI: confidence interval; CJD; Creutzfeldt-Jakob disease; FN: false negative; FP: false positive; NPV: negative predictive value; OS: overall survival; PPV: positive predictive value; QC: quality control; SLNB: sentinel lymph node biopsy; SLNB RR: sentinel lymph node biopsy reduction rate; TN: true negative; TP: true positive

^a SLNB reduction rate (SLNB RR) = $([TN+FN]/[TP+TN+FP+FN])$: proportion of patients classified CP-GEP Low Risk who could forgo SLNB

Limitations of the clinical validity studies are listed in Table 20 and 21.

Table 20. Clinical Validity Study Relevance Limitations of the Merlin Test

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Mulder et al (2021) ^{82,}		3. Algorithm tested on bridged qPCR platform (QuantstudioDx) rather than development platform (Fluidigm)	3. Not compared to MSKCC, MIA, or other clinicopathologic nomograms		1. No long-term follow-up outcomes
Yousaf et al (2021) ^{83,}			3. Not compared to MSKCC, MIA, or other clinicopathologic nomograms		1. No long-term recurrence or survival data reported

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Johansson et al (2022) ⁸⁴ ,					1. No long-term outcome follow-up data
Stassen et al (2023) ⁸⁵ ,			3. Not compared to MSKCC, MIA, or other clinicopathologic nomograms		1. No long-term recurrence or survival follow-up reported
Pazhava et al (2025) ⁸⁸ ,			3. Not compared to MSKCC, MIA, or other clinicopathologic nomograms.		
Amaral et al (2025) ⁵² ,			2. No SLNB reference standard available	2. No actionable management pathway for high-risk stage I–IIA exists	
Zijlker et al (2025) ⁸⁶ ,					
Weitemeyer et al (2025) ⁸⁷ ,				1. No health outcomes (survival) reported; diagnostic performance only	1. No follow-up for survival outcomes
Hieken et al (2025) ⁵¹ ,			2. No centralized pathology review; SLN positivity definitions varied by institution		1. Long-term survival outcomes pending

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 21. Clinical Validity Study Design and Conduct Limitations of the Merlin Test

Study	Selection^a	Blinding^b	Test Delivery^c	Selective Reporting^d	Data Completeness^e	Statistical^f
Mulder et al (2021) ^{82,}		1.Process for blinding pathologist to CP-GEP result during SLN re-evaluation not fully described.			2.28.6% eligible patients excluded due to inability to retrieve FFPE	2. Comparison to other tests not reported.
Yousaf et al (2021) ^{83,}	2. Electronic pathology searches and chart reviews	1. Blinding between SLNB and CP-GEP results not explicitly described; randomization/blinding process not stated.			2.Limited sample sizes within individual T-stage subgroups producing wide confidence intervals	2. Comparison to other tests not reported.
Johansson et al (2022) ^{84,}					2. 13.1% patients excluded; primary reasons include FFPE unavailability from remote laboratories (n=42) and insufficient tissue (n=12). 63 patients (15%) could not be assessed by both nomograms due to missing covariates.	
Stassen et al (2023) ^{85,}					2. 14.6% patients who did not undergo SLNB excluded	2. Comparison to other tests not reported.
Pazhava et al (2025) ^{88,}	2. Patients selected from previously reported larger cohorts		4. Each site followed its own SLNB guidelines during			2. Comparison to other tests not reported.

Study	Selection ^a	Blinding ^b	Test Delivery ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
			the study period.			
Amaral et al (2025) ⁵² ,	2. Retrospective ; archival FFPE tissue	1. No blinding possible; retrospective	2. Timing of CP-GEP analysis relative to clinical events not described		2. 63 excluded for QC failures (6.3%)	
Zijlker et al (2025) ⁸⁶ ,	2. Retrospective ; sample from biobank	1. CP-GEP not blinded to SLNB (retrospective)				
Weitemeyer et al (2025) ⁸⁷ ,					2. 330 excluded for missing DMD data (registry issue)	
Hieken et al (2025) ⁵¹ ,	2. Surgeon selected enrollment			1. Study registration details not reported in manuscript	2. 380 individuals excluded (~22%)	

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 (ie, 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.

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.

For the proposed use of the test as a triage for SLN biopsy (identify patients who can avoid SLN biopsy), performance characteristics are well-characterized as indicated by prospective and retrospective studies. However, given that the primary objective of the double-blinded prospective study conducted by Hieken et al (2025) ⁵¹, was not achieved and that a low-risk CP-GEP result does not reduce a patient's SN metastasis risk below the guideline-based threshold for omitting SLNB, no inferences can be made about clinical utility through a chain of evidence.

SECTION SUMMARY: GENE EXPRESSION PROFILING TO GUIDE MANAGEMENT DECISIONS IN MELANOMA

DecisionDx

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 (ie, 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.⁵⁰ 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.

Merlin Test

To use prognostic information for decision-making, performance characteristics should be consistent and precise. As the intended use of this assay is to select stage I and II patients who can avoid sentinel lymph node (SLN) biopsy, then the test should identify a group who are eligible for SLN biopsy but have low risk of recurrence. Given that the primary objective of the largest prospective evaluation was not achieved, no link to connect risk stratification to management decisions to health outcomes (no actionable treatment pathway for stage I–IIA high-risk patients), and the substantial heterogeneity within the retrospective validation studies, no chain of evidence for clinical utility can be created due to lack of robust evidence of clinical validity and lack of a 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.⁸⁹ 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 (eg, 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 (eg, sentinel lymph node eligibility, follow-up, and/or therapeutic choice) is not recommended outside of a clinical study or trial."

The American Academy of Dermatology's Choosing Wisely recommendation states 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.⁹⁰ The Academy noted that early, thin melanoma (melanoma in situ, T1a melanoma or T1b melanoma < 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 (v1.2026) for cutaneous melanoma made the following statements on use of GEP: ⁹¹,

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 tests to differentiate benign from malignant melanocytic neoplasms include immunohistochemistry (IHC) and molecular testing via comparative genomic hybridization (CGH), fluorescence in situ hybridization (FISH), gene expression profiling (GEP), single-nucleotide polymorphism (SNP) array, and next-generation sequencing (NGS). These tests may facilitate a more definitive diagnosis and guide therapy in cases that are diagnostically uncertain or controversial by histopathology. Ancillary tests should be used as adjuncts to clinical and expert dermatopathologic examination and therefore be interpreted within the context of these findings."

The guidelines state the following regarding prognostic testing:

" Based on the current evidence, the NCCN Melanoma Panel does not recommend incorporation of commercially available prognostic GEP tests into melanoma care. The routine use of GEP to predict patient outcome 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. Moreover, since there is a low probability of metastasis in stage IA melanoma and a high proportion of false-positive results using these tests, GEP testing should not guide clinical decision-making in this subgroup. "

"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 (eg, sex, age, primary tumor location, thickness, ulceration, mitotic rate, lymphovascular invasion, microsatellites, and/or SLNB status). Furthermore, the clinical utility of these tests to inform treatment recommendations and improve health outcomes by prompting an intervention has not been established. 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 tests."

"Regarding predictive GEP for SLNB risk, findings of the prospective Merlin_001 trial suggest that CP-GEP testing may be used in select patients with T1b ± T2a melanoma to support shared decision-making (NCCN 2A recommendation), when a patient or provider would decide against SLNB if the true risk was <10%. A high-risk result in that scenario would portend a 3 times higher risk of SLN involvement based on trial results. Prospective study of the utility of predictive GEP for SLNB risk, in conjunction with risk prediction models that incorporate well-established CP factors, is ongoing."

"Alternative GEP tests for SLNB risk prediction are not recommended outside of the context of a clinical study or trial based on current data. Additional prospective investigation and outcomes data (including impact of missing a positive SLNB) will further inform the utility of GEP tests, multivariable nomograms/risk calculators (eg, melanomarisks.org.au/snlnd; [mskcc.org/nomograms/melanoma/sentinel lymph node metastasis](http://mskcc.org/nomograms/melanoma/sentinel_lymph_node_metastasis)), and other decision analytical models for SLNB risk prediction. Existing GEP tests for SLNB risk prediction should be prospectively compared with no-cost, contemporary models that incorporate readily available CP variables."

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.⁹² 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)

Society of Surgical Oncology

In 2025, a panel of melanoma experts from the Society of Surgical Oncology convened to develop recommendations regarding the use of GEP to guide management of patients with melanoma.⁹³ Currently available GEP tests were assessed in 3 clinical pathways; "(1) the utility in patient selection for sentinel lymph node biopsy; (2) the utility to guide surveillance; and (3) the utility to inform adjuvant therapy." The following are consensus recommendations regarding the use of GEP tests to guide management of individuals with melanoma:

"GEP testing is not currently recommended for routine use in predicting sentinel lymph node (SLN) status. There is a lack of high-level evidence regarding changing indications for SLNB based on GEP results.

GEP testing is not currently recommended to guide a specific surveillance or follow-up approach in melanoma care.

GEP testing is not currently recommended to replace SLNB for prognostication or staging, or to guide surveillance and adjuvant treatment approaches in patients (AJCC pT1b-pT4b) who are otherwise recommended for the procedure."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in March 2026 did not identify any ongoing or unpublished trials that would likely influence this review.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
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; Decision Dx
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 tissue, algorithm reported as a categorical result (i.e., benign, indeterminate, or malignant)
0314U	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 35 genes (32 content and 3 housekeeping), utilizing formalin-fixed paraffinembedded (FFPE) tissue, algorithm reported as a categorical result (i.e., benign, intermediate, malignant)
0578U	Oncology (cutaneous melanoma), RNA, gene expression profiling by real-time qPCR of 10 genes (8 content and 2 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reports a binary result, either low-risk or high-risk for sentinel lymph node metastasis and recurrence

REVISIONS	
07-23-2018	Policy added to the bcbsks.com web site on June 22, 2018 with an effective date of July 23, 2018.
02-01-2019	Updated Description section.
	Updated Rationale section.
	Updated References section.
07-01-2019	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Added new CPT codes: 0089U, 0090U.
	Updated References section.
03-11-2021	Updated Description section.
	Updated Rationale section.

REVISIONS	
	Updated References section.
07-02-2021	Updated Description section.
	Updated Rationale section.
	In the Coding section Added CPT code 81529 (effective 01-01-2021)
	Updated References section.
04-01-2022	Updated Coding Section Added 0314U, 0315U (new codes 04-01-2022)
07-12-2022	Updated Description Section
	Updated Rationale Section
	Updated References Section
06-27-2023	Updated Description Section
	Updated Rationale Section
	Updated Coding Section - Removed ICD-10 Diagnosis Box - Removed 81479, 81599, 84999, 0315U
	Updated References Section
06-27-2024	Updated Description Section
	Updated Rationale Section
	Updated References Section
07-08-2025	Updated Description Section
	Updated Rationale Section
	Updated References Section
Posted 07-14-2026 Effective 08-13-2026	Updated Description Section
	Updated Policy Section Added Statement D: Gene expression testing, including but not limited to Merlin test, in the evaluation of individuals with cutaneous melanoma is considered experimental / investigational.
	Updated Rationale Section
	Updated Coding Section Add Code 0578U
	Updated Reference Section

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