Gene Expression Profiling for Cutaneous Melanoma

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DESCRIPTION

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

Melanoma is a cancer that begins in the melanocytes. Other names for this cancer include malignant melanoma and cutaneous melanoma. Most melanoma cells still make melanin, so melanoma tumors are usually brown or black. But some melanomas do not make melanin and can appear pink, tan or even white. Melanomas can develop anywhere on the skin, but they are more likely to start on the trunk (chest and back) in men and on the legs in women. The neck and face are other common sites.

Risk factors for melanoma include skin type, personal history of prior melanoma, multiple clinically atypical moles or dysplastic nevi, a positive family history of

melanoma, and rarely, inherited genetic mutations. Genetic counseling could be considered for individuals with a strong family history of invasive melanoma with or without pancreatic cancer. In addition to genetic factors, environmental factors including excess sun exposure and UV-based artificial tanning contribute to the development of melanoma. The interaction between genetic susceptibility and environmental exposure is illustrated in individuals with an inability to tan and fair skin that sunburns easily who have a greater risk of developing melanoma. However, melanoma can occur in any ethnic group and, also in areas of the body without substantial sun exposure.

As with nearly all malignancies, the outcome of melanoma depends on the stage at presentation. In the United States, it is estimated that 84% of patients with melanoma initially present with localized disease, 9% with regional disease, and 4% with distant metastatic disease. In general, the prognosis is excellent for patients who present with localized disease and primary tumors 1.0 mm or less in thickness, with 5-year survival achieved in more than 90% of patients. For patients with localized melanomas more than 1.0 mm in thickness, survival rates range from 50% to 90% depending on tumor thickness, ulceration and miotic rate. The likelihood of regional nodal involvement increases with increasing tumor thickness, as well as the presence of ulceration and miotic rate. When regional nodes are involved, survival rates are roughly halved.

There is increasing appreciation of the variations in specific genetic alternations among distinct clinical subtypes of melanoma. Currently described clinical subtypes of cutaneous melanoma are non-chronic sun damage (non-CSD); melanoma on skin without chronic sun-induced damage; CSD: melanomas on skin with chronic sun-induced damage signified by the presence of marked elastosis; and acral; melanomas of the soles, palms, or sub-ungual sites.

Different subtypes of melanoma have been found to have very different genetic profiles, some of which have different therapeutic implications. Ina n analysis of 102 primary melanomas, the non-CSD subtype was found to have the highest proportion of BRAF mutations (56%) compared to CSD, acral and mucosal types (6%, 21% and 3% respectively). On the other hand, incidence of KIT aberrations was 28%, 36%, and 39% in CSD, acral and mucosal subtypes, respectively, but 0% in non-CSD subtypes. NRAS mutations were found in 5% to 20% of the subtypes.

Primary care physicians evaluate suspicious pigmented lesions to determine who should be referred to dermatology considering both a patient's risk factors for melanoma as well as visual examination of the lesion. The visual examination assesses whether the lesion has features suggestive of melanoma. Criteria for features suggestive of melanoma have been developed. One checklist is the ABCDE checklist:

- Asymmetry
- Border irregularities
- Color variegation
- Diameter $\geq$ 6 mm
- Evolution

Standard of care for the assessment of clinically suspicious pigmented skin lesions is surgical biopsy and subsequent histopathology. However, histopathology is believed to have inherent limitations. Some lesions that are likely to be true melanomas based on clinical behavior do not meet the complete set of histologic criteria to establish a melanoma diagnosis. There is also considerable interrater variability with visual image and pattern recognition of skin lesions. In an effort to improve patient survival, several novel noninvasive techniques have been developed to classify pigmented skin lesions at an earlier stage.

Commercially Available Gene Expression Profiling (GEP)

- **DecisionDx Melanoma (Castle Biosciences):** DecisionDx- Melanoma is a gene expression profile (GEP) test that was designed to identify the risk of recurrence or metastasis in Stage I, II and III melanomas based on the biological profile of 31 genes (28 prognostic genes and 3 control genes) within a patient's tumor tissue.

  The test is used to:
  - Inform patients individual treatment plan; and
  - Whether to perform the SLNB surgical procedure; and
  - Determining the appropriate level of follow-up, imaging and referrals.

  DecisionDx-Melanoma is performed on formalin-fixed, paraffin embedded (FFPE) primary tumor tissue from either a biopsy or excision.

- **DiffDx-Melanoma (Castle Biosciences):** Is a 35-gene expression profile test to aid dermatopathologists in characterizing difficult-to-diagnose melanocytic lesions by providing a result of either benign, intermediate-risk or malignant using two proprietary algorithms applied to the gene expression patterns to identify the malignant potential of a lesion, giving dermatologists more information to improve patient management decisions regarding lesions located on the head and neck.

- **myPath Melanoma (Myriad Genetics, Inc):** Per the manufacturer's website myPath melanoma test is used as an adjunct to histopathology when the distinction between a benign nevus and a malignant melanoma cannot be made by histopathology alone. The test measures 23 genes for which expression patterns differ between malignant melanoma and benign nevi. These genes are involved in cell differentiation, cell signaling, and immune response signaling. The genes included in myPath Melanoma testing are:

  - PRAMER a single gene involved in cell differentiation
  - S100A7, S100A8, S100A9, S100A12 and P13, a group of genes involved in multiple cells signaling pathways

- CCL5, CD38, CXCL10, CXCL9, IRF1, LCP2, PTPRC and SELL involved in tumor immune response signaling
- Nine housekeeping gene that are measured to normalize RNA expression for analysis CLTC, MRFAPI, PPP2CA, PSMA1, RPL13A, RPL8, RPS29, SLC25A3 and TXNLI

An algorithm is applied that combines measurements of gene expression, assigns a weight to each gene component and establishes a threshold value. The result is a single numerical score that classifies a melanocytic lesion as "likely benign", "likely malignant" or "indeterminant."

- **Pigmented Lesion Assay (PLA) (DermTech):** Per the manufacturers website the Pigmented Lesion Assay (PLA) is a non-invasive gene expression tests to identity subtle malignancy changes thereby enhancing early melanoma detection. Using adhesive patches, skin tissue is sampled across an entire lesion. RNA is extracted from the collected skin cells and RT-PCR is used to assess the expression analysis of two genes, PRAME and LINC00518 allows DermTech to distinguish between melanoma and non-melanoma. DermTech's PLA can aid in the physician's biopsy decision. The test is intended on pigmented lesion suspicious for melanoma that the physical would like additional information prior to surgical biopsy.

  - PLA Uses Include:
    - Lesion that meets one or more ABCDE criteria
    - Lesion being followed for change
    - Lesions in sensitive areas
    - Lesion on patients with potential risks to surgical biopsy including patients who are anti-coagulated, at risk for infection, and at risk for poor wound healing or elevated abnormal scarring
    - Lesions on patients what are needle averse or biopsy fatigued
  - PLA negative lesions are generally monitored
  - PLA positive lesions are generally surgically biopsied to establish diagnosis

Gene Expression Profiling to Guide Initial Biopsy Decisions

Clinical Content and Test Purpose

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

Populations

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

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

Interventions

The test being considered is the DermTech Pigmented Lesion Assay (PLA). 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).

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

The Pigmented Lesion Assay test report includes 2 results. The first result is called the PLA MAGE (Melanoma Associated Gene Expression), which indicates low-risk (neither PRAME nor LINC00518 expression was detected), moderate-risk (expression of either PRAME or LINC00518 was detected), or high-risk (expression of both PRAME 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.

It is not clear whether the Pigmented Lesion Assay test is meant to be used as a replacement, triage, or add-on test with respect to dermoscopy. The Pigmented Lesion Assay sample report states that for low-risk lesions, physicians should "consider surveillance," while for moderate- and high-risk lesions, physicians should "recommend a biopsy." It does not state whether lesions with negative results should be further evaluated with dermoscopy or other techniques to confirm the lesion should not be biopsied. Therefore, this evidence review evaluates the test as a replacement for dermoscopy. Currently there is a low threshold for biopsy of suspicious lesions. As such,

tests that can rule-out need for biopsy could be useful and thus sensitivity and negative predictive value are the performance characteristics of most interest.

Comparators
After a referral from primary care to dermatology settings, dermatologists use visual examination as well as tools such as dermoscopy to make decisions regarding biopsy of suspicious lesions. A meta-analysis of 9 studies (8487 lesions with 375 melanomas) compared dermoscopy with visual examination alone for the diagnosis of melanoma; it reported that, for clinicians with training in dermoscopy, adding dermoscopy to visual examination increased the sensitivity from 71% to 90%. The specificity numerically increased from 80% to 90%, but the difference was not statistically significant. 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.

The reference standard for diagnosis of melanoma is histopathology.

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

The harmful outcome of a false-positive result is having an unnecessary biopsy. The harmful outcome of a false-negative result is potential delay in diagnosis and treatment. The timeframe of interest for calculating performance characteristics is time to biopsy result. Patients who forgo biopsy based on test results could miss or delay diagnosis of cancer. Longer follow-up would be necessary to determine the effects on overall survival.

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

Determining whether a test can guide biopsy decisions is not based only on its sensitivity and specificity, but also on how the accuracy of the existing pathway for making biopsy decisions is changed by the test. Therefore, the appropriate design for evaluating performance characteristics depends on the role of the new test in the pathway for making biopsy decisions. New tests may be used as replacements for existing tests, to triage who proceeds for existing tests or add-on tests after existing tests. For replacement tests, the diagnostic accuracy of both tests should be concurrently compared, preferably in a paired design (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.

Multiple high-quality studies are needed to establish the clinical validity of a test. The PLA test has one clinical validity study with many methodologic and reporting limitations (Gerami et. al. 2017). Therefore, performance characteristics are not well-characterized. Also, the test has not been compared with dermoscopy, another tool frequently used to make biopsy decisions.

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 individuals receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

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).

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. Forty-five dermatologists evaluated 60 clinical and dermoscopic images of atypical pigmented lesions (8 melanoma, 52 nonmelanoma). In the first round, dermatologists did not have Pigmented Lesion Assay test results and, in the second round, dermatologists had access to Pigmented Lesion Assay test results with the order of cases being scrambled. The dermatologists were asked whether the lesions should be biopsied after each round. Therefore, the corresponding number of biopsy decisions should be 45×60×2=5400. Data were collected in 2014 and 2015. Results were reported for 4680 decisions with no description of the disposition of the remaining decisions. Of the 4680 reported decisions, 750 correct biopsy decisions were made without Pigmented Lesion Assay results while 1331 were made with Pigmented Lesion Assay results and 1590 incorrect biopsy decisions were made without Pigmented Lesion Assay results while 1009 incorrect biopsy decisions were made with Pigmented Lesion Assay results.

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.

A Molecular Test Assessment completed by Hayes September 2019 determined there is a potential but unproven benefit regarding the use of Pigmented Lesion Assay (PLA) to accurately differentiate melanoma lesions from nonmelanoma lesions. Some of the published evidence suggests that the safety and impact on health outcomes are at least comparable to standard of care treatment and testing, but uncertainty remains about the safety and/or impact on health net outcomes due to the poor quality of studies, limited data, and conflicting study results. Long term studies are needed to demonstrate whether the performance of Pigmented Lesion Assay (PLA) clearly demonstrate the performance

of this assay is at least as good as or better than the current standard of care of visual assessment followed by surgical biopsy and histopathology as needed.

Summary of Evidence
The evidence is currently insufficient to support the use of the Pigmented Lesion Assay (PLA) to accurately differentiate melanoma lesions from nonmelanoma lesions. Study limitations include the small study populations, lack of generalizability of study results to more diverse melanoma subtypes, lack of blinding primary readers, as well as early reports of insufficient RNA obtained from study samples. Independent prospective clinical utility studies are currently lacking, and it is unclear if the use of PLA versus conventional diagnostic tools lead to changes in health care decision making and improvements in patient survival. Current practice standards and clinical management guidelines do not include the use of gene expression profiling for suspicious pigmented lesions. Gene expression profiling testing for melanoma is not recommended outside of clinical trials. Additional well-designed randomized controlled trials (RCTs) in larger patient populations with diverse melanoma subtypes are needed to add to the evidence based and corroborate the early study findings. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Gene Expression Profiling for Diagnosing Lesions with Indeterminate Histopathology or Difficulty Diagnosis

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

Populations
The relevant population of interest is individuals whose melanocytic lesion is indeterminate based on clinical and histopathologic features or to aid dermatopathologists in characterizing difficult-to-diagnose melanocytic lesions for diagnosis.

Interventions
The tests being considered is the Myriad myPath Melanoma test to distinguish malignant melanoma from benign nevus and DiffDx-Melanoma (Castle Biosciences) to assist dermatopathologists with characterizing lesions that are difficult to diagnose.

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

Comparative genomic hybridization and FISH are also used to diagnosis indeterminate lesions.

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 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 treatment of melanoma, at least five years of event-free follow-up is required to confirm negative tests. The event of interest is metastasis.

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).

myPath Melanoma Test
Multiple high-quality studies are needed to establish the clinical validity of a test. The myPath test has one clinical validity study including long-term follow-up for metastasis as the reference standard. However, it is not clear whether the study population included lesions that were indeterminate following histopathology and the study had other methodologic and reporting limitations. Therefore, performance characteristics are not well-characterized.

DiffDx-Melnaoma
Multiple high-quality studies are needed to establish the clinical validity of a test. The DiffDx-Melanoma has one clinical validity study (Estrada et. al. 2020) which was utilized to validate the 35-GEP in an independent set of 273 benign and 230 malignant formalin-fixed, paraffin-embedded (FFPE) pigmented tissue lesions collected from multiple independent dermatopathology laboratories as part of this Institutional Review Board (IRB)-approved study. The 35-GEP test to distinguish benign from malignant pigmented lesions was developed to improve diagnostic accuracy and reduce diagnostic uncertainty for difficult-to-diagnose cases. The test demonstrated 99.1% sensitivity, 94.3% specificity, 93.6% positive predictive value and 99.2% negative predictive value. 96.4% of cases received a differential result and 3.6% had intermediate risk. Limitations of this study are 3.6% of the cases fell into an intermediate risk zone which is reflective of a molecular biology of both benign and malignant lesions and interpretation of an intermediate-risk result of the 35-GEP should be considered in the context of other clinicopathological information. It would be of great diagnostic importance to exclude the possibility of

sampling error and ensure that the entire clinical lesion has been evaluated by routine histopathology which is standard of care. Also, there may be bias related to this study as SIE is a consultant and shareholder of Castle Biosciences.

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 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).

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.

myPath Melanoma Test
Two decision-impact studies assessed the potential impact of myPath on physicians' treatment decisions in patients with diagnostically challenging lesions. Given the lack of health outcomes, it is not known whether any treatment changes were clinically appropriate.

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.

A Molecular Test Assessment by Hayes May 2018 regarding myPath Melanoma (Myriad Genetics) determined there is insufficient published evidence to assess the safety and/or impact on health outcomes or patient management. While there was some promising information on the use of myPath Melanoma more studies evaluating clinical utility are needed to add to this evidence. These studies should also include how dermatologists use this test result in conjunction with other clinical information to arrive at the treatment management of the individual.

DiffDx-Melanoma
In a decision-impact study by Farberg et. al. 2020, dermatopathologists (n=6) and dermatologists (n=14) were queried regarding diagnostic challenges and patient management strategies in 60 difficult-to-diagnose melanocytic neoplasms. Participants reviewed each lesion twice, once without the 35-GEP result and once with. Responses were evaluated for consistent trends in the utilization of the 35-GEP test result. Dermatopathologists utilized the 35-GEP result to refine their diagnoses in lesions receiving a benign versus malignant. Dermatopathologists indicated that 30.3% of lesions were diagnostically very challenging or challenging, while 40.3% were considered very easy or easy. Overall, diagnostic confidence was increased (51%), while additional work-up requests were decreased in cases with benign 35-GEP (72.1%) and increased with

malignant 35-GEP (45.6%) results. Dermatologists utilized the 35-GEP result to gauge overall prognosis which was increased in 76.2% of responses for cases with a benign 35-GEP result and decreased in 94.2% of cases with malignant 35-GEP result. Case difficulty was increased in 54% of responses with a malignant 35-GEP result and decreased in 25% if a benign 35-GEP result was provided. Alterations in office visit frequency (25.9% increase in benign vs. 95.2% increase in malignant 35-GEP result) and re-excisions (76.7% decrease in re-excision in benign vs. 44.5% increase in re-excision in malignant 35-GEP result) were also influenced by the 35-GEP result. While this impact study showed promise in refining the diagnosis of melanocytic neoplasms head-to-head comparisons with other GEP tests for melanoma diagnosis do not exist and further comparative randomized controlled trials are warranted to determine the clinical utility related to this testing. Also, there may be bias related to this study KLA, CNB, BHR, KD, CJ, OZ, and RWC are employees and shareholders of Castle Biosciences, Inc.

Summary of Evidence
For individuals who have melanocytic lesions with indeterminate histopathologic features who receive gene expression profiling (GEP) with the myPath Melanoma test added to histopathology to aid in diagnosis of melanoma, the evidence includes retrospective and prospective observational studies. No direct evidence of clinical utility was identified. Current practice standards and clinical management guidelines do not include the use of gene expression profiling for melanocytic lesions with indeterminate histopathologic features. Gene expression profiling testing for melanoma is not recommended outside of clinical trials. Additional well-designed randomized controlled trials (RCTs) are needed to compare diagnosis and health outcomes of those evaluated with histopathology alone and those with myPath Melanoma as an adjunct to histopathology. The evidence is insufficient to determine the effects of the technology on net health outcomes.

For individuals who have difficult to diagnose melanocytic lesions who receive gene expression profiling (GEP) with the DiffDX- Melanoma the current evidence is limited, and why a decision impact study may have showed promise no direct evidence of clinical utility was identified. Current practice standards and clinical management guidelines do not include the use of gene expression profiling for melanocytic lesions for diagnosis. Gene expression profiling testing for melanoma is not recommended outside of clinical trials. Additional well-designed randomized controlled trials (RCTs) are needed to compare DiffDx-Melanoma with other GEP tests to determine diagnosis and health outcomes of those evaluated with histopathology alone (standard of care) and those with DiffDX-Melanoma as an adjunct to histopathology. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Gene Expression Profiling to Guide Management Decisions in Melanoma

Clinical Context and Test Purpose
Many treatments and surveillance recommendations are based on AJCC tumor, node and metastatic staging system. Individuals may also undergo sentinel lymph node biopsy (SLNB) to gain more definitive information about the status of the regional nodes.

Wide local excision is the definitive surgical treatment of melanoma. Following surgery, patients with AJCC stage I or II (node-negative) melanoma do not generally receive adjuvant therapy. Patients with higher risk melanoma receive adjuvant immunotherapy or targeted therapy. Ipilimumab has been shown to prolong recurrence-free survival (RFS) by approximately 25% compared with placebo at a median of 5.3 years in patients with resected, stage III disease. Nivolumab has been shown to further prolong survival compared with ipilimumab by approximately 35% at 18 months. 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.

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

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

At least 3 uses for the test have been suggested. One clinical validity study, the authors stated that "high-risk patients with stage I and II disease may benefit from adjuvant therapy and/or enhanced imaging protocols to allow for early detection of metastasis.' In another clinical validity study, the authors concluded that the test's "role in consideration of patients for adjuvant therapy should be examined prospectively. This use of the test would be as a replacement for SLN biopsy since SLN biopsy is currently used to identify patients 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-T2)"
2. "Deciding what level of follow-up, imaging, and referrals are appropriate for any patient with a tumor at least 0.3 mm deep."

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

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

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

Interventions
The test being considered is the Castle Biosciences DecisionDx-Melanoma test. The DecisionDx test measures expression of 31 genes using quantitative reverse-transcription polymerase chain reaction. The test includes 28 prognostic gene targets and 3 endogenous control genes. The test is performed on standard tissue sections from an existing formalin-fixed, paraffin-embedded biopsy or wide local excision specimen.

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

Comparators
Treatment and surveillance recommendations are based on AJCC staging. SLNB may be used to get more definitive information about the status of the regional nodes compared with a physical examination. The American Society of Clinical Oncology and National Comprehensive Cancer Network have similar but not identical recommendations regarding which patients should undergo SLNB based on thickness and other high-risk features.

SLNB has a low rate of complications.

Online tools are available to predict prognosis based on the AJCC guidelines.

Outcomes
Regarding selecting individuals for adjuvant therapy and/or enhanced surveillance:
If the test is used to 'rule-in' AJCC stage I or IIA patients, a negative DecisionDx (class 1) test result would not change outcomes. Per guidelines, the patients would not receive adjuvant therapy or enhanced surveillance, just as without the DecisionDx test. A positive DecisionDx (class 2) test result would indicate that a patient might benefit from adjuvant therapy or enhanced surveillance. Therefore, the potential beneficial outcomes of a true positive result are additional treatment and surveillance and potentially prolonged survival. The potential harmful outcomes of a false-positive result are unnecessary adverse effects and burdens of adjuvant therapy and enhanced surveillance.

Regarding patients who would benefit from enhanced surveillance in AJCC stage IIB to III patients:

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

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

Regarding selecting AJCC stage I to IIA individuals who can avoid SLNB:
For individuals meeting guideline-recommended criteria for SLNB, a positive DecisionDx (class 2) test result would not change outcomes. The patients would proceed to SLNB, as they would have without the DecisionDx test, and treatment and imaging decisions would depend on SLNB results. A negative DecisionDx (class 1) test result in patients 55 years of age and older who have tumors less than 2 mm deep (T1-T2) would indicate that a patient could avoid an SLNB. Therefore, the potential beneficial outcomes of a true-negative result are avoidance of an SLNB 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.
The risk of recurrence decreases over time but does not reach 0.

A Molecular Test Assessment by Hayes March 2022 regarding DecisionDx-Melanoma (Castle Biosciences) that determined there is insufficient published evidence to assess the safety and/or impact on health outcomes or patient management. No studies were identified regarding clinical utility of DecisionDx-Melanoma to inform patient management decisions and improve outcomes for patients with AJCC stage I, II or III cutaneous melanoma. Additional studies are also needed to demonstrate the clinical validity of this test on its ability to predict risk of recurrence and the risk of recurrence, metastasis and/or SNL positivity.

Summary of Evidence
Treatment plans for cutaneous melanoma are based upon individual risk of recurrence. Decisions made post-diagnosis include recommendation for sentinel lymph node biopsy (SNLB), followed by management decisions such as surveillance, frequency of follow-up, and interdisciplinary consultations including possible adjuvant therapy use. These have traditionally been guided by clinicopathologic factors, but discordance exists, as melanoma deaths have occurred in patients diagnosed with disease considered to be early stage by such factors, including a negative SLNB. Gene expression profiling (GEP) testing to include DecisonDx-Melanoma has been proposed to optimize patient care as a

predictor of risk of recurrence, distant metastasis and death in stage I-III melanoma and assist in guiding SLNB decisions. While studies have shown some promise in certain clinical situations, current practice standards and clinical management guidelines at this time do not indicate the use of gene expression profiling for the management of cutaneous melanoma. The National Society of Cutaneous Medicine in 2019 published appropriate use criteria for the integration of diagnostic and prognostic gene expression profile assays for management of cutaneous melanoma. 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. The 2019 guideline by the American Academy of Dermatology (AAD) regarding care for the management of primary cutaneous melanoma states the following: "There is insufficient evidence to recommend routine molecular profiling assessment for baseline prognostication. Evidence is lacking that molecular classification should be used to alter patient management outside of current guidelines (e.g., NCCN and AAD). The criteria for and the utility of prognostic molecular testing, including GEP, in aiding clinical decision making (e.g., SLNB eligibility, surveillance intensity, and/or therapeutic choice) needs to be evaluated in the context of clinical study or trial." The National Comprehensive Cancer Network (NCCN) Cutaneous Melanoma Version 3.2022 guideline recommendation states the following: "While there is interest in new prognostic molecular techniques such as gene expression profiling to help differentiate benign from malignant neoplasms, or to help distinguish melanomas at low-versus high-risk for metastasis, routine (baseline) genetic testing of primary cutaneous melanomas (before or following SLN biopsy [SLNB] is not recommended outside of a clinical study." Additional well-designed randomized controlled trials (RCTs) are needed to determine the clinical utility of gene expression profiling of cutaneous melanoma compared with traditional clinical factors to guide medical management and improve clinical outcomes to include established follow-up schedules. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Practice Guideline and Position Statements

National Comprehensive Cancer Network (NCCN)
Cutaneous Melanoma Version 3.2022

Footnotes for Clinical Presentation, Pathology Report and Preliminary Workup
The use of gene expression profiling (GEP) testing according to specific AJCC-8 melanoma stage (before or after SLNB) requires further prospective investigation in large, contemporary data sets of unselected patients. Prognostic GEP testing to differentiate melanomas at low versus high risk for metastasis should not replace pathologic staging procedures. Moreover, since there is a low probability of metastasis in stage I (T1) melanoma and higher proportion of false-positive results, GEP testing should not guide clinical decision making in this subgroup. On an individual basis, the likelihood of a positive SLNB may be informed by the use of optimized multivariable

nomograms/risk calculators and ongoing investigation of GEP tests. *See Principles of Molecular Testing.*

Principles of Molecular Testing: Emerging Molecular Technologies for Cutaneous Melanoma Diagnosis and Prognostication

Diagnostic Testing for Indeterminate Melanocytic Neoplasms Following Histopathology

- Melanocytic neoplasm of uncertain biologic potential presents 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 interpretation of 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.

Prognostic Testing

- Commercially available GEP tests are marketed as being able to classify cutaneous melanoma into separate categories based on risk of metastasis. However, it remains unclear whether these GEP platforms clinically actionable prognostic information when combined or compared with known clinicopathologic factors or multivariable nomograms/risk calculators that incorporate patient sex, age, tumor location and thickness, ulceration, mitotic rate, lymphovascular invasion, microsatellites, and SLNB status. Furthermore, the impact of these tests on treatment outcomes or follow-up schedules has not been established.
- Various studies of prognostic GEP testing suggest its role as an independent predictor of worse outcome, though not superior to Breslow thickness or SNL status. It remains unclear whether available GEP tests are reliably predictive of outcome across the risk spectrum of melanoma. Prospective validation studies (similar to those performed in breast cancer) are required to more accurately define the clinical utility of molecular prognostics of GEP testing as an adjunct to traditional staging or as part of the multidisciplinary decision-making process, its role in guideline surveillance imaging, SLNB, and adjuvant therapy.
- Existing and emerging GEP tests and other prognostic molecular techniques (i.e., ctDNA testing), should also be compared with optimized contemporary multivariable phenotypic models (e.g., melanomarisk.org.au) and the AJCC 8th Edition melanoma decision-tree analysis in development.

Somatic Mutation Testing

- A number of somatic genetic alterations have been identified in cutaneous melanoma, a few of which are targetable driver mutations that have proven useful to guide treatment decisions and/or clinical trial eligibility.

Biopsy: NCCN Recommendations

Patients presenting with suspicious pigmented lesions optimally should undergo an excisional biopsy (elliptical, punch, or saucerization), preferably with 1to 3 mm negative margins. The orientation of the excisional biopsy should always be planned with definitive treatment in mind (e.g., a longitudinal orientation in the extremities parallel to lymphactics). With the increasing use of lymphatic mapping and sentinel node biopsy, biopsies should also be planned so as not to interfere with the procedure. In this regard, wider margins for the initial diagnostic procedure should be avoided.

Excisional biopsy may be inappropriate for certain sites (including the face, palmar surface of the hand, sole of the foot, ear, distal digit, or sublingual lesion) or for very large lesions. In these instances, a full-thickness incisional or punch biopsy of the clinically thickest portion of the lesion is an acceptable option. These procedures should provide accurate primary tumor microstaging, without interfering with definitive local therapy. If the initial biopsy is inadequate to make a diagnosis or accurately microstage the tumor (based on evaluation by a dermatopathologist) for treatment planning, re-biopsy with narrow margin excision should be considered. Shave biopsy may compromise pathologic diagnosis and complete assessment of Breslow thickness. However, it is acceptable in a low suspicion setting.

Molecular Characterization of the Primary Tumor

Comparative genomic hybridization (CGH) or fluorescence in situ hybridization (FISH) may be helpful in detecting the presence of selected gene mutations for histologically equivocal lesions. CGH is a more comprehensive technique than FISH that may offer higher sensitivity and specificity in identifying relevant copy number changes, as suggested by a small study on atypical Spitz tumors.

In addition to CGH and FISH, a number of diagnostic or prognostic genetic tests for melanoma are in development. One of these commercially available gene expression profiling tests was developed to help predict the biologic behavior of atypical melanocytic lesions with indeterminate histopathology (e.g., melanocytic or Spitz tumors of uncertain malignant potential). Although there is a tremendous clinical need for this technology, the challenges of developing a truly discriminant test are substantial. Even in the presence of sentinel lymph node (SLN) metastasis these indeterminate neoplasms can demonstrate a strikingly benign biologic behavior, making it exceedingly difficult to define a true positive (fully malignant lesion). Furthermore, as the very few events in this low-risk group tend to be late, long-term follow-up is required to validate the prognostic significance of this test.

Another currently commercially available gene expression profiling test is being marketed to supplement prognostic information derived from the primary tumor and SNLs. This technique was developed to discriminate patients at low risk versus high risk for metastatic disease based on the different expression of 28 genes. The gene set was developed from a relatively high-risk training set of patients and tested in a different relatively high-risk validation set of patients. This gene expression profile has been validated as independently predictive of outcome when compared to AJCC stage or SLN status. This test has not been directly evaluated in the context of all known prognostic characteristics of localized melanoma. Furthermore, its independent prognostic value has yet to be confirmed in a large population of patients with average – to low-risk melanoma.

Gene expression profiling for melanoma could be an enormously valuable contribution to understanding the biology of the disease. However, the difficulty of embracing gene expression profiling as an independent predictor of outcome is illustrated by the inconsistency of results across studies aimed at defining the most predictive gene sets for melanoma. Comparison of the gene signatures identified in these studies show minimal overlap in specific genes thought to be predictive of outcome. The identification and validation of a prognostic gene expression profile is a complicated multi-step and often multi-step process, and there are many ways in which specifics of study design and methodology can impact the end result. The lack of overlap in gene signatures identified as prognostic for melanoma is likely due to substantial differences in study design and methodology. Efforts to develop gene expression profiling prognostic assays for other types of cancer have also resulted in limited for partial overlap in the "gene signature" identified by different studies.

Pathology Report: NCCN Recommendations
While there is interest in new prognostic molecular techniques such as gene expression profiling to help differentiate benign from malignant neoplasms, or to help distinguish melanomas at low-versus high-risk for metastasis, routine (baseline) genetic testing of primary cutaneous melanomas (before or following SLN biopsy [SLNB] is not recommended outside of a clinical study.

American Academy of Dermatology
In 2019, the American Academy of Dermatology updated their 2011 guideline regarding care for the management of primary cutaneous melanoma which states:
Recommendations for baseline and surveillance studies and follow-up:

- Baseline radiologic imaging and laboratory studies are not recommended for asymptomatic patients with newly diagnosed stage 0-II primary CM.
- Radiologic imaging and laboratory studies for CM at baseline should be performed only to evaluate specific signs or symptoms of synchronous metastasis (regional nodal or distant).
- The use of LN ultrasound is encouraged at baseline or in surveillance in the setting of an equivocal LN on physical examination, and for surveillance when
    - The patient meets criteria for SLNB but does not undergo the procedure;

    - SLNB is not possible or not technically successful (e.g., because of failure of lymphoscintigraphic dye migration and inability to identify a draining SLN); or
    - CLND is not performed in the setting of a positive SLNB; and
    - When radiology expertise in the use of nodal ultrasound surveillance for CM is available.
- Regular clinical follow-up is recommended as the most important means of detecting CM recurrence. Findings from the history (review of systems) and physical examination should direct the need for further radiologic or laboratory studies to detect local, regional, and distant metastatic disease.
- Collaboration with medical oncology is recommended for patients with high-risk CM (stage IIB and IIC) and those with a positive SLNB result for discussion of surveillance imaging and clinical comanagement.
- Surveillance follow-up schedule and consideration of radiographic imaging varies according to the risk of disease recurrence (as determined by stage of disease and other factors) and risk of new primary CM (determined by mole pattern, presence of atypical nevi, and family history). Laboratory studies are not recommended for surveillance of asymptomatic patients with CM.
- Patient education on self-examination of the skin and LN for the detection of recurrent disease or new primary CM is recommended.
- There is insufficient evidence to recommend routine molecular profiling assessment for baseline prognostication. Evidence is lacking that molecular classification should be used to alter patient management outside of current guidelines (e.g., NCCN and AAD). The criteria for and the utility of prognostic molecular testing, including GEP, in aiding clinical decision making (e.g., SLNB eligibility, surveillance intensity, and/or therapeutic choice) needs to be evaluated in the context of clinical study or trial.

Regulatory Status
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory developed tests must meet the general regulatory standards of the clinical laboratory Improvement Amendments. The Pigmented Lesion Assay, myPath Melanoma, and DecisionDX-Melanoma 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.

PRIOR APPROVAL

Not applicable.

POLICY

See also the following medical policies:

- 02.04.53 Gene Expression Profiling for Uveal Melanoma
- 02.04.41 Genetic Testing for Familial Cutaneous Malignant Melanoma

Gene expression profiling (GEP) testing in the evaluation of individuals with suspicious pigmented lesions, including but not limited to Pigmented Lesion Assay (PLA) is considered **investigational**. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Gene expression profiling (GEP) testing in the evaluation of individuals with melanocytic lesions with indeterminate histopathologic features, including but not limited to myPath Melanoma test is considered **investigational**. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Gene expression profiling (GEP) testing in the evaluation of individuals with difficult-to-diagnose melanocytic lesions including but not limited to DiffDx-Melanoma is considered **investigational.** The evidence is insufficient to determine the effects of the technology on net health outcomes.

Gene expression profiling (GEP) testing in the evaluation of individuals with cutaneous melanoma as a predictor of risk of recurrence, distant metastasis and death in stage I-III melanoma and assist in guiding SLNB decisions, including but not limited to DecisionDx-Melanoma is considered **investigational**. The evidence is insufficient to determine the effects of the technology on net health outcomes.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 81479 Unlisted molecular pathology procedure
- 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-embeded tissue, algorithm reported a recurrence risk, including likelihood of sentinel lymph node metastasis (DecisionDX Melanoma)
- 81599 Unlisted multianalyte assay with algorithmic analysis procedure
- 84999 Unlisted chemistry procedure
- 0089U Oncology (melanoma), gene expression profiling by RT-PCR, PRAME and LINC00518, superficial collection using adhesive patch(es) (Pigmented Lesion Assay (PLA) DermTech)

- 0090U Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin-embedded (FEPE) tissue, algorithm reported as categorical result (i.e., benign, indeterminate, malignant) (myPath Melanoma)
- 0134U Oncology (cutaneous melanoma) mRNA gene expression profiling by RT-PCR of 35 genes (32 content and3 housekeeping), utilizing formalin-fixed paraffin-embedded 9FFPE) tissue, algorithm reported as a categorical result (i.e., benign, intermediate, malignant) (DiffDx-Melanoma)

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POLICY HISTORY

Date	Reason	Action
May 2022	Annual Review	Policy Revised
May 2021	Annual Review	Policy Renewed
May 2020	Annual Review	Policy Revised
May 2019	Annual Review	Policy Renewed
May 2018		New Policy Created

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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