SKIN

CLINICAL MANAGEMENT RECOMMENDATIONS

Appropriate Use Criteria for the Integration of Diagnostic and Prognostic Gene Expression Profile Assays into the Management of Cutaneous Malignant Melanoma: An Expert Panel Consensus-Based Modified Delphi Process Assessment

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The last century has seen a vast increase in the incidence of malignant melanoma, both in the United States and worldwide.[1] In 2019, an estimated 96,480 cases of invasive melanoma will be diagnosed in the United States alone, resulting in over 7,000 deaths.[2]

Advances in basic and translational research are essential in addressing this public health challenge. Developments in molecular biology and genomics are rapidly expanding the armamentarium of diagnostic and therapeutic tools available to facilitate the management of melanoma patients.[3] A deeper understanding of patterns of gene expression in melanoma lesions has resulted in the development of novel tests designed to both aid in the diagnosis of melanoma and to provide additional prognostic information in confirmed cases. These gene expression profiling (GEP) assays utilize a quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR) to determine the level of expression of key groups of signature genes.[4-6] The utility of diagnostic and prognostic GEP technology is based upon the fact that the level of expression of key genes varies between benign and malignant pigmented lesions and between malignant melanomas with lower and higher propensity for subsequent metastasis, respectively.[4-6] Depending on the specific test being utilized, the results can aid in the decision to biopsy equivocal pigmented lesions[6], assist dermatopathologists in determining a diagnosis in cases of challenging

histopathology[7], and provide managing clinicians with further prognostic information in cases of biopsy-proven melanoma.[4]

In 2018, three validated, US governmentally approved, commercially available GEP tests were each incorporated into melanoma patient management over 10,000 times in the United States.[8-11] Despite the magnitude of melanoma GEP test utilization, current melanoma management guidelines—including those recently put forward by the American Academy of Dermatology (AAD)—fail to provide guidance regarding the use of these assays across specific clinical situations.[12] Given the existing knowledge gap and the high current magnitude of utilization of these tests, there is a critical need for an evidence-based consensus statement. To meet this need, a panel of dermatologists/dermatopathologists with expertise in pigmented lesions, knowledge of the melanoma-related GEP literature, and/or experience with appropriate use criteria (AUC) consensus development was convened to systematically review the available evidence surrounding CLIA-certified GEP diagnostic and prognostic tests. The objective of this expert panel was to develop a set of consensus-based AUC recommendations to guide the integration of GEP technology into the diagnosis and management of melanoma in specifically-defined situations commonly encountered in clinical practice.

METHODS

Selection of GEP Assays for Inclusion

It was specified *a priori* that these recommendations would pertain to clinically diagnostic, histologically diagnostic, or prognostic GEP assays for melanoma that were validated, US governmentally approved for clinical use, readily available, and with existing widespread usage at the time the expert panel was convened. This led to selection of three GEP assays which met inclusion criteria: the 2-GEP test[6] (Pigmented Lesion Assay, DermTech, La Jolla, CA), the 23-GEP test[5] (myPath®, Myriad Genetics, Inc., Salt Lake City, UT), and the 31-GEP test[4] (DecisionDx™-Melanoma, Castle Biosciences, Inc., Friendswood, TX).

GEP augmenting melanoma clinical diagnosis

The 2-GEP test is an adjunctive diagnostic assay used to aid the clinician in the decision to biopsy in cases of clinically and/or dermoscopically equivocal pigmented lesions. Genetic material (in the form of RNA) is harvested from the lesion in question by an adhesive patch. The RNA is then reverse-transcribed to DNA and amplified using qRT-PCR to determine RNA expression levels of two key genes: long intergenic non-protein coding RNA 518 (LINC00518) and melanoma antigen preferentially expressed in tumors (PRAME).[6] The method is non-invasive and yields a low, moderate, or high-risk result for each lesion tested. This result is then considered in the context of lesion morphology, clinical history, and data from other adjunctive tests to determine if biopsy or continued observation is warranted.

GEP augmenting melanoma histopathological diagnosis

The 23-GEP test is a diagnostic assay utilized by dermatopathologists to aid in rendering a final diagnosis in cases where histopathologic features alone cannot fully distinguish between benign and malignant melanocytic lesions.[5] RNA is extracted from formalin-fixed, paraffin-embedded biopsy

specimens and qRT-PCR is used to assess expression of 23 key genes. These genes, involved in cell differentiation, cell-cell signaling, and immune response, have expression patterns which vary between benign nevi and malignant melanoma in a predictable manner. The results are combined into a single score ranging from -16.7 through 11.1, with groupings corresponding to benign, indeterminate, or consistent with malignant melanoma.[5]

GEP augmenting assessment of melanoma prognosis

The 31-GEP test, as opposed to the 2-GEP and 23-GEP assays, is used to help determine prognosis in patients with early-stage invasive cutaneous melanoma. After extraction of RNA from formalin-fixed, paraffin-embedded excision specimens of primary melanoma, the level of expression of 31 genes (28 prognostic genes) is quantified using qRT-PCR and used to stratify patients into low-risk (Class 1a and 1b) and high-risk (Class 2a and 2b) groups based on probability of subsequent metastasis.[13,14] The results of this test have been shown to be synergistic with existing risk-stratification tools identifying patients with high-risk tumors.[13,15]

Literature Search

A thorough systematic review of the literature pertaining to the use of the 2-, 23-, and 31-GEP tests was conducted. The goal of this search was to identify studies evaluating either clinical validity, outcomes, or utility for level of evidence review and development of recommendations by the expert panel. The Medline database was queried for all relevant articles published between 1940 and 2018 using exploded MeSH terms and keywords pertaining to the following themes: gene expression profiling, diagnosis, prognosis, and molecular genomics. The Boolean term “AND” was used to find the intersection of these themes with the term “cutaneous melanomas.”

The initial search identified potentially relevant articles, which were each distributed to reviewers who independently screened for relevance and appropriateness for inclusion. The articles that remained were then assessed in depth to determine relevance to the study objective and final eligibility. Discrepancies between the independent reviewers were resolved through team discussion. Articles deemed relevant to one of the three GEP tests being evaluated based on full-text review were selected for level of evidence analysis by members of the consensus panel.

Development of Consensus-Based AUC Recommendations

An initial list of potential indications for the use of each GEP test was created based on review of the pertinent articles identified through the literature search as well as the clinical experience of a core group of experts. This list was meant to encompass a broad selection of clinical scenarios commonly faced by practicing dermatologic surgeons and dermatopathologists in the diagnosis and management of melanocytic lesions. The purpose was to identify common scenarios in which utilization of GEP tests might be considered so that the existing literature could be assessed for evidence supporting or refuting their use in each situation. This list was not meant to be inclusive of every possible situation for which the use of the 2-, 23-, or 31-GEP tests could be considered, but was meant to cover a wide range of the most common scenarios. After initial creation of the list of indications for each GEP assay, each member of the consensus panel had an

opportunity to review and propose modifications of the draft indications.

Level of Evidence Assessment and Consensus Recommendation Process

A consensus panel of nine expert dermatologists/dermatologic surgeons/dermatopathologists selected for their knowledge of the tests being evaluated and the associated literature, their expertise in managing pigmented lesions, and/or their recognized academic excellence was convened in person in August 2018, to determine the individual level of evidence for each of the selected publications as well as an overall strength of recommendation for each indication using standard Strength of Recommendation Taxonomy (SORT) methodology.[16] The selected articles were made available for individual review prior to the consensus meeting. Additionally, a reference offering an overview of the SORT framework[16] was provided and a brief lecture on evidence-based medicine and SORT methodology was delivered to members of the expert panel.

Consensus among panel members regarding level of evidence for each article and strength of recommendation for each recommendation was achieved using a modified Delphi technique.[17] This methodology has been used extensively in the literature to yield recommendations for dermatologists.[18-20] Consensus was defined as agreement among at least a supermajority of 2/3 of the experts participating in the panel. If 2/3 agreement could not be achieved, the proposal was re-discussed among panel members and modified until agreement was achieved.

RESULTS

Comprehensive Literature Search

The initial literature search produced 524 articles. After review of articles deemed potentially relevant, 33 articles which measured the clinical validity, relevance, efficacy, and/or utility of the GEP tests were designated for distribution to the full consensus panel. Of the 33 relevant published articles identified, 8 pertained to the 2-GEP test[6,21-27], 10 were pertinent to the 23-GEP test[5,7,28-35], and 15 were germane to the 31-GEP test[13-15,36-47] (Tables 1-3).

Levels of Evidence of Selected Articles

Where applicable, SORT guidelines were utilized to assign a level of evidence to each article based on consensus of the expert panel as outlined previously (Tables 1-3). Of the 8 articles pertaining to the 2-GEP test, 2 were determined by expert panel consensus to represent Level 3 evidence[25,26], 2 were deemed consistent with Level 2 evidence[21,22], and 2 were felt to represent Level 1 evidence[6,23]. Two articles were not assigned levels of evidence because after group discussion, consensus deemed their content irrelevant to the generated list of recommendations.[10,27]

Based on the consensus of the expert panel, 2 of the 10 articles pertaining to the 23-GEP test were felt to represent Level 3 evidence[33,35], 4 were deemed to be consistent with Level 2 evidence[7,30,31,34], and 3 were determined to be Level 1 evidence.[5,29,32] One article was not assigned a level of evidence because it was deemed irrelevant to the current study.[28]

Regarding the published articles detailing the 31-GEP test, 3 out of 15 were deemed to represent Level 3 evidence[37,40,46], 9 were classified as Level 2 evidence[14,15,36,38,41,42,44,45,47], and 2 graded as Level 1 evidence[13,43]. Upon discussion by the expert panel, 1 article was deemed to be outside of the context of the panel and thus was not assigned a level of evidence.[39] Overall, consensus opinion was reached on the strength of recommendation for 29 recommendations involving the use of diagnostic and prognostic gene expression profiling tests in the diagnosis and management of melanoma (Tables 4-6).

Consensus-Based AUC Recommendations for the 2-GEP Test

Of the 7 recommendations considered for the 2-GEP test (Table 4), 1 was deemed to represent a B-strength recommendation for the use of the 2-GEP assay:

- Cases in which patients present with atypical lesions requiring additional assessment beyond inspection in order to aid in the biopsy decision

Six were deemed to represent a C-strength recommendation:

- Cases in which patients refuse surgical biopsy
- Cases in which suspicious lesions present in cosmetically sensitive areas
- Cases in which patients have undergone numerous biopsies in the past and wish to avoid additional biopsy procedures
- Scenarios in which patients have a relative contraindication to surgical biopsy
- Patients with increased risk of infection (e.g. immunosuppressed patients)
- Patients with heightened risk of poor wound healing

Consensus-Based AUC Recommendations for the 23-GEP Test

For the 23-GEP test, expert consensus was reached on 8 recommendations (Table 5).

One recommendation received an A-strength consensus recommendation based on the existing published evidence:

- Differentiation of a nevus from melanoma in an adult patient when the morphologic findings are ambiguous by light microscopic parameters

Three scenarios for the use of the 23-GEP test received a B-strength recommendation:

- Cases with pathology suggestive or suspicious for nevoid melanoma vs. benign melanocytic nevus
- Cases with pathology suggestive or suspicious for atypical Spitz tumor vs. Spitzoid melanoma
- Instances in which pathology is suggestive of or suspicious for severely atypical compound melanocytic proliferation vs melanoma on cosmetically sensitive areas

Four recommendations received a C-strength recommendation:

- Instances of pathology suggestive or suspicious for melanoma arising from within a severely dysplastic nevus
- Cases of pathology suggestive or suspicious for benign vs. malignant blue nevus
- To differentiate suspicious lesions in low-risk populations

- Upon request from the referring dermatologist following an ambiguous pathology report

Consensus-Based AUC Recommendations for the 31-GEP Test

A total of 14 recommendations were considered for clinical use of the 31-GEP test, and expert consensus was reached on each scenario (Table 6).

One of 14 received an A-strength recommendation:

- Use of the 31-GEP test to aid in the management of patients who are SLNBx negative

Seven of the recommendations received a B-strength recommendation:

- Integration of 31-GEP results into the decision to adjust follow-up frequency
- Integration of 31-GEP results into the decision to order adjunctive imaging studies
- Integration of 31GEP results into management of patients with T1a tumors with Breslow depth <0.8 mm and other adverse prognostic factors
- Integration of 31-GEP results into management of patients with T1 or T2 tumors who are sentinel lymph node biopsy (SLNBx) eligible
- Integration of 31-GEP results into management of patients with T1b tumors
- Integration of 31-GEP results into management of patients with T2 tumors
- Integration of 31-GEP results into management of patients with a low-risk category based on traditional AJCC factors

Six received a C-strength recommendation:

- Integration of 31-GEP results into the assessment of prognosis and management options for patients with T1a tumors with a positive deep margin
- Integration of 31-GEP results into the assessment of prognosis and management options for patients with T1b tumors with a positive deep margin
- Integration of 31-GEP results to for risk-stratification of patients in clinical trials
- Use of 31-GEP results as a criterion for eligibility for a chemotherapy regimen
- T4 disease as a contraindication for use of the 31-GEP test
- Melanoma *in situ* as a contraindication for use of the 31-GEP test

DISCUSSION

This study is significant because it represents the first set of expert consensus-based AUC recommendations developed for the usage of diagnostic and prognostic gene expression profiles in the management of suspicious pigmented/melanocytic lesions and biopsy-proven melanoma. The recommendations offered herein stratify the strength of evidence available for commonly encountered potential indications for the three validated, CLIA-certified, readily available GEP tests currently available for use in the diagnosis and management of malignant melanoma. Previous guidelines have either not commented on the use of GEP assays[48] or have made broad statements concerning diagnostic and prognostic genetic tests without offering any detailed discussion about defined use in

specific clinical situations.[12] Given that these diagnostic and prognostic GEP assays are clinically available and are each already being used in over 10,000 cases per year[8-11], it is critical to provide clinicians with a set of evidence-based criteria to help ensure that these tests are used for clinically indicated situations.

It is imperative that practicing clinicians interpreting these consensus-based recommendations understand the underlying methodology, which led to their creation. The expert consensus panel that determined the strength of each recommendation for GEP usage understood that not all cases encountered in the clinical setting will align perfectly with these pre-defined scenarios. These recommendations are meant to provide a framework that can be applied to the majority of clinical scenarios and which can be used as a starting point to provoke thoughtful decision making in situations not specifically defined by the evaluated scenarios. This aligns with the original definition of evidence-based medicine, which notes the individual clinician's responsibility in critically appraising the literature to permit thoughtful case-specific decision making and assist in patient counseling.[49]

It is also important that clinicians have an appropriate understanding of the meaning of each recommendation grade as defined by the SORT taxonomy.[16] Although an A-strength recommendation represents the highest level of support, even a C-strength recommendation (typically based upon disease-oriented evidence, expert opinion or usual practice) does provide appropriate direction for use in specific situations. Studies rated as B or C level evidence are generally accepted as appropriate for establishing clinical recommendations when A level evidence is not available.

Along these lines, the juxtaposition of the dynamic nature of research with the often static nature of AUC recommendation statements must be considered when interpreting these findings. It therefore must be understood by clinicians utilizing these recommendations that the body of available evidence is not static and is constantly evolving. Often, governmental bodies and large agencies lag in recognizing the value of new technologies because of lengthy review processes and delays in academic publishing. This study attempted to mitigate these complications by providing the most up-to-date body of evidence, including articles published even a week before the consensus panel was convened. In such a rapidly evolving field, the impetus for this panel was to make recommendations that will affect current dermatologist management. However, the expert consensus panel that developed these recommendations understands and is optimistic that research in this field will continue to evolve. It is therefore the hope of the panel that these recommendations will be updated as new evidence emerges.

There are several limitations to this study. Only 3 GEP tests were considered because they are the only validated, CLIA-certified, and widely used tests currently available. Other tests may be available in the future that may supersede the efficacy of the current tests. An additional limitation, consistent with most publications focusing on recommendations, is that the panel did not consider costs in the analysis. This would have been difficult as healthcare costs in the United States depend on a variety of factors including market factors and policies inherent to specific insurance plans. However, several studies have been published supporting the cost-effectiveness of these tests,[24,50] and more will likely be undertaken in the future. In addition, in

many situations, GEP tests are now covered by Medicare and other insurance plans, and assistance from industry is often available, capping the associated costs and facilitating the accessibility of these assays to patients in need.

CONCLUSION

These expert consensus-based AUC recommendations present an evidence-based framework developed through systematic literature review and expert consensus for applying diagnostic and prognostic GEP tests to the management of melanoma patients. Clinical judgment should be applied to the use of these recommendations, and decisions regarding the use of GEP should be made on an individual, case-by-case basis. Additional studies aiming to fill these gaps will refine these findings and will be important in the development of updated consensus recommendations.

DISCLAIMER

These expert panel consensus-based AUC recommendations have been developed for the purpose of guiding clinical decision making regarding the use of gene expression profiles in the management of malignant melanoma. It should be recognized that these consensus-based recommendations are based on the best available evidence at the time that these recommendations were made, in combination with expert opinion. These recommendations are intended to be fluid and may evolve over time as new gene expression evidence profile tests become available and as new evidence regarding existing assays is published. These recommendations are not all-inclusive and should not be expected to definitively address all possible clinical situations faced by dermatologists and dermatologic surgeons. These recommendations were developed with the intent of aiding clinical decision making, but the final judgment as to the utility of any specific diagnostic or prognostic test in a specific situation must be made by the managing physician while considering all data available.

Conflict of Interest Disclosures:
Brian Berman, MD PhD: Castle BioSciences-Consultant.
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Tables

Table 1: Level of evidence for articles related to 2 GEP test.

Reference	Level of Evidence
Lee N, Scope A, Rabinovitz H. Assessing Skin Cancer Using Epidermal Genetic Information Retrieved by Adhesive Patch Skin Surface Sampling. Dermatol Clin. 2017;35(4):521-524.	3
Wachsman W, Morhenn V, Palmer T, et al. Noninvasive genomic detection of melanoma. Br J Dermatol. 2011;164(4):797-806.	N/A
Gerami P, Yao Z, Polsky D, et al. Development and validation of a noninvasive 2-gene molecular assay for cutaneous melanoma. J Am Acad Dermatol. 2017;76(1):114-120.e2.	1
Jansen B, Hansen D, Moy R, Hanhan M, Yao Z. Gene Expression Analysis Differentiates Melanomas from Spitz Nevi. J Drugs Dermatol. 2018;17(5):574-576.	3
Ferris LK, Moy RL, Gerami P, et al. Noninvasive Analysis of High-Risk Driver Mutations and Gene Expression Profiles in Primary Cutaneous Melanoma. J Invest Dermatol. 2019; 139(5):1127-1134.	1
Ferris LK, Gerami P, Skelsey MK, et al. Real-world performance and utility of a noninvasive gene expression assay to evaluate melanoma risk in pigmented lesions. Melanoma Res. 2018;	2
Ferris LK, Jansen B, Ho J, et al. Utility of a Noninvasive 2-Gene Molecular Assay for Cutaneous Melanoma and Effect on the Decision to Biopsy. JAMA Dermatol. 2017;153(7):675-680.	2
Hornberger J, Siegel DM. Economic Analysis of a Noninvasive Molecular Pathologic Assay for Pigmented Skin Lesions. JAMA Dermatol. 2018; 154:1025-31.	N/A

Table 2: Level of evidence for articles related to 23 GEP test.

Reference	Level of Evidence
Leachman SA, Mengden koon S, Korcheva VB, White KP. Assessing Genetic Expression Profiles in Melanoma Diagnosis. Dermatol Clin. 2017;35(4):537-544.	3
Warf MB, Flake DD, Adams D, et al. Analytical validation of a melanoma diagnostic gene signature using formalin-fixed paraffin-embedded melanocytic lesions. Biomark Med. 2015;9(5):407-16.	3
Clarke LE, Warf MB, Flake DD, et al. Clinical validation of a gene expression signature that differentiates benign nevi from malignant melanoma. J Cutan Pathol. 2015;42(4):244-52.	1
Clarke LE, Flake DD, Busam K, et al. An independent validation of a gene expression signature to differentiate malignant melanoma from benign melanocytic nevi. Cancer. 2017;123(4):617-628.	1
Clarke LE, Pimentel JD, Zalaznick H, Wang L, Busam KJ. Gene expression signature as an ancillary method in the diagnosis of desmoplastic melanoma. Hum Pathol. 2017;70:113-120.	2
Ko JS, Matharoo-ball B, Billings SD, et al. Diagnostic Distinction of Malignant Melanoma and Benign Nevi by a Gene Expression Signature and Correlation to Clinical Outcomes. Cancer Epidemiol Biomarkers Prev. 2017;26(7):1107-1113.	1
Reimann JDR, Salim S, Velazquez EF, et al. Comparison of melanoma gene expression score with histopathology, fluorescence in situ hybridization, and SNP array for the classification of melanocytic neoplasms. Mod Pathol. 2018;	2
Cassarino DS, Lewine N, Cole D, Wade B, Gustavsen G. Budget impact analysis of a novel gene expression assay for the diagnosis of malignant melanoma. J Med Econ. 2014;17(11):782-91.	N/A
Cockerell CJ, Tschen J, Evans B, et al. The influence of a gene expression signature on the diagnosis and recommended treatment of melanocytic tumors by dermatopathologists. Medicine (Baltimore). 2016;95(40):e4887.	2
Cockerell C, Tschen J, Billings SD, et al. The influence of a gene-expression signature on the treatment of diagnostically challenging melanocytic lesions. Per Med. 2017;14(2):123-130.	2

Table 3: Level of evidence for articles related to 31 GEP test.

Reference	Level of Evidence
Farberg AS, Glazer AM, Winkelmann RR, Rigel DS. Assessing Genetic Expression Profiles in Melanoma Prognosis. Dermatol Clin. 2017;35(4):545-550.	3
Sidiropoulos M, Obregon R, Cooper C, Sholl LM, Guitart J, Gerami P. Primary dermal melanoma: a unique subtype of melanoma to be distinguished from cutaneous metastatic melanoma: a clinical, histologic, and gene expression-profiling study. J Am Acad Dermatol. 2014;71(6):1083-92.	2
Gerami P, Cook RW, Russell MC, et al. Gene expression profiling for molecular staging of cutaneous melanoma in patients undergoing sentinel lymph node biopsy. J Am Acad Dermatol. 2015;72(5):780-5.e3.	1
Gerami P, Cook RW, Wilkinson J, et al. Development of a prognostic genetic signature to predict the metastatic risk associated with cutaneous melanoma. Clin Cancer Res. 2015;21(1):175-83.	2
Ferris LK, Farberg AS, Middlebrook B, et al. Identification of high-risk cutaneous melanoma tumors is improved when combining the online American Joint Committee on Cancer Individualized Melanoma Patient Outcome Prediction Tool with a 31-gene expression profile-based classification. J Am Acad Dermatol. 2017;76(5):818-825.e3.	2
Hsueh EC, Debloom JR, Lee J, et al. Interim analysis of survival in a prospective, multi-center registry cohort of cutaneous melanoma tested with a prognostic 31-gene expression profile test. J Hematol Oncol. 2017;10(1):152.	1
Cook RW, Middlebrook B, Wilkinson J, et al. Analytic validity of DecisionDx-Melanoma, a gene expression profile test for determining metastatic risk in melanoma patients. Diagn Pathol. 2018;13(1):13.	3
Greenhaw BN, Zitelli JA, Brodland DG. Estimation of Prognosis in Invasive Cutaneous Melanoma: An Independent Study of the Accuracy of a Gene Expression Profile Test. Dermatol Surg. 2018;	2
Zager JS, Gastman BR, Leachman S, et al. Performance of a prognostic 31-gene expression profile in an independent cohort of 523 cutaneous melanoma patients. BMC Cancer. 2018;18(1):130.	2
Gastman BR, Gerami P, Kurley SJ, et al. Identification of patients at risk for metastasis using a prognostic 31-gene expression profile 3 in subpopulations of melanoma patients with favorable outcomes by standard criteria. J Am Acad Dermatol. J Am Acad Dermatol. 2019 Jan;80(1):149-157.	2
Berger AC, Davidson RS, Poitras JK, et al. Clinical impact of a 31-gene expression profile test for cutaneous melanoma in 156 prospectively and consecutively tested patients. Curr Med Res Opin. 2016;32(9):1599-604.	2
Farberg AS, Glazer AM, White R, Rigel DS. Impact of a 31-gene Expression Profiling Test for Cutaneous Melanoma on Dermatologists' Clinical Management Decisions. J Drugs Dermatol. 2017;16(5):428-431.	N/A
Dillon LD, Gadzia JE, Davidson RS, et al. Prospective, Multicenter Clinical Impact Evaluation of a 31-Gene Expression Profile Test for Management of Melanoma Patients. SKIN. 2018;2(2).	2
Schuitevoerder D, Heath M, Cook RW, et al. Impact of Gene Expression Profiling on Decision-Making in Clinically Node Negative Melanoma Patients after Surgical Staging. J Drugs Dermatol. 2018;17(2):196-199.	2
Svoboda RM, Glazer AM, Farberg AS, Rigel DS. Factors Affecting Dermatologists' Use of a 31-Gene Expression Profiling Test as an Adjunct for Predicting Metastatic Risk in Cutaneous Melanoma. J Drugs Dermatol. 2018;17(5):544-547.	3

Table 4: Consensus-based recommendations for utilization of the 2 GEP test.

Recommendation	Strength[a]
Patients that refuse surgical biopsy	C
Lesions present in cosmetically sensitive areas	C
Patients with relative contraindications to surgical biopsy such as anticoagulation or anesthetic sensitivity	C
Patients with wound healing risk (e.g. excessive or hypertrophic scarring or prolonged healing)	C
Patients with increased infection risk (immunosuppressed patients)	C
Patients with atypical lesions requiring assessment beyond visual inspection to help in selection for biopsy	B
Patients who have undergone numerous biopsies in the past who don't want additional biopsies	C

[a]Based on SORT Taxonomy, A = Consistent, good-quality patient-oriented evidence, B = Inconsistent or limited-quality patient-oriented evidence, C = Consensus, disease-oriented evidence, usual practice, expert opinion, or case series

Table 5: Consensus-based recommendations for utilization of the 23 GEP test.

Recommendation	Strength[a]
Differentiation of a nevus from melanoma in an adult patient when the morphologic findings are ambiguous by light microscopic parameters	A
Pathology suggestive or suspicious for nevoid melanoma vs. benign melanocytic nevus	B
Pathology suggestive or suspicious for melanoma arising within a severely dysplastic nevus	C
Pathology suggestive or suspicious for malignant blue nevus vs. benign blue nevus	C
Pathology suggestive or suspicious for atypical Spitz tumor vs. Spitzoid melanoma	B
Pathology suggestive or suspicious for severely atypical compound melanocytic proliferation vs melanoma on cosmetically sensitive areas and special sites, including digits, acral, genital, ears and scalp	B
Differentiate suspicious lesions in low risk populations	C
For the dermatologist to request after ambiguous pathology report	C

[a]Based on SORT Taxonomy, A = Consistent, good-quality patient-oriented evidence, B = Inconsistent or limited-quality patient-oriented evidence, C = Consensus, disease-oriented evidence, usual practice, expert opinion, or case series

Table 6: Consensus-based recommendations for utilization of the 31 GEP test.

Recommendation	Strength[a]
Integrating 31GEP results into assessing prognosis and management options for patients with:	
- T1a tumors in whom there is significant uncertainty about the adequacy of microstaging (positive deep margin)	C
- T1b+ tumors in whom there is significant uncertainty about the adequacy of microstaging (positive deep margin)	C
Integrating 31 GEP results into the decision:	
- To adjust follow up regimens	B
- To assess need for imaging	B
Integrating 31GEP results into managing patients:	
- With T1a tumors with Breslow depth <0.8 mm and with other adverse features (eg. very high mitotic index [≥2/mm2], lymphovascular invasion, or a combination of these factors)	B
- With T1 and T2 cutaneous melanoma who are sentinel lymph node biopsy (SLNBx) eligible	B
- With T1b tumors (≥ 0.8 mm or < 0.8 mm with ulceration)	B
- With T2 tumors	B
Integrating 31GEP results into subsequent management of patients:	
- Who are sentinel node negative	A
- Who are in AJCC “low risk” categories: (Thin (<1mm), Stage I-IIA, SLNBx-)	B
Integrating 31GEP results into randomizing patients in clinical trials for risk stratification (randomization)	C
Integrating 31GEP results as a criteria for inclusion in a chemotherapy regimen	C
Contraindications:	
- Do not perform 31GEP in patients with T4 disease	C
- Do not perform in patients with melanoma in situ	C

[a]Based on SORT Taxonomy, A = Consistent, good-quality patient-oriented evidence, B = Inconsistent or limited-quality patient-oriented evidence, C = Consensus, disease-oriented evidence, usual practice, expert opinion, or case series