SKIN

Clinical Management Recommendations

Incorporating Prognostic Gene Expression Profile Assays into the Management of Cutaneous Melanoma: An Expert Consensus Panel Report

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ABSTRACT

Background: Cutaneous melanoma (CM) guidelines put forth by the eighth edition of the American Joint Committee on Cancer (AJCC8) and the National Comprehensive Cancer Network (NCCN) do not currently account for lesion genomics when assessing prognosis. Gene Expression Profile (GEP) tests have become a widely adopted tool to help clinicians identify patients at higher risk for metastasis and recurrence.
Objective: To review the available literature that has been published since a consensus panel in 2018 on three commercially available GEP tests used in the prognostic assessment of CM and create updated guidelines and consensus statements for their optimal use.
Methods: A comprehensive literature search of PubMed and Google Scholar was conducted for relevant English-language original research articles, meta-analyses, and systematic reviews published from 2019 through 2022. A panel of 6 key opinion leaders in dermatology with specialized expertise in diagnosing and managing CM then convened to review the articles and create guidelines. A modified Delphi process was used to approve each statement. The panel assigned each article a level of evidence and each consensus statement a strength of recommendation using Strength of Recommendation Taxonomy (SORT) criteria.
Results: The literature search identified 785 articles that met the search criteria. Of these, there were 22 articles that validated the 31-GEP test, 2 that validated the 11-GEP test, and 7 that validated the 8-GEP + CP test. The panel unanimously approved 6 usage guidelines and 5 consensus supporting statements for the appropriate use of these tests.
Conclusion: Based on the currently available literature, GEP tests provide valuable information beyond AJCC8 and NCCN guidelines for the prognostic assessment of CM. There are significantly more validation studies supporting the use of the 31-GEP test compared to the 11-GEP test and the 8-GEP + CP test.

INTRODUCTION

The incidence of cutaneous melanoma (CM) is increasing faster than any other malignancy.[1] Early detection is paramount, as prognosis is significantly impacted by stage at diagnosis. With traditional prognostic assessment using the eighth edition of the American Joint Committee on Cancer (AJCC8), stage I CM has a 10-year overall survival (OS) of 94 to 98% while stage IV disease has a 10-year OS of 10 to 15%.[2]

The development and validation of gene expression profile (GEP) assays that use a quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR) to identify the level of expression of certain groups of signature genes has significantly advanced cancer prognostic assessment.[3-8] Because the level of expression of these signature genes varies between benign and malignant lesions as well as lesions that have a lower or higher likelihood for metastasis, these tests can provide important prognostic information. In addition, studies have demonstrated that genomics can identify a high-risk subset of CM patients with stage I and II disease that are at greater risk for recurrence, metastasis, and increased mortality based on their lesions' genetic profile.[3-5]

Tens of thousands of CM GEP tests are currently being ordered annually in the US to aid clinicians in their prognostic assessment of patients with CM.[9] However, current CM staging according to AJCC8 as well as guidelines put forth by the National Comprehensive Cancer Network (NCCN) do not formally incorporate GEP test data to further stratify patients. Berman et. al reviewed the literature available through 2018 to provide clinical management recommendations on the use of GEP tests for CM diagnosis and prognosis.[10] The purpose of this current expert consensus panel was to review the multiple studies published subsequent to that paper on the validity, accuracy, and utility of commercially available CM GEP prognostic tests to provide updated guidance on their usage.

METHODS

Selection of GEP Assays

It was specified prior to the review that the recommendations would be based on prognostic GEP assays for CM that have published studies evaluating validity and efficacy, are commercially available, and used regularly. This resulted in the selection of 3 GEP tests that met inclusion criteria: the 31-GEP test (DecisionDx™-Melanoma, Castle Biosciences, Inc.), the 11-GEP test (MelaGenix, NeraCare GmbH), and the 8-GEP + CP test (Merlin, SkylineDx, B.V.).

31-GEP Test

The 31-GEP test is a CM prognostic assay that measures the level of expression of 28 target genes and three control genes in order to stratify CM into low-risk (class 1A), intermediate risk (class 1B/2A), and high-risk (class 2B) categories based on risk of recurrence, metastasis and probability of sentinel lymph node biopsy (SLNB) positivity.[3] The test utilizes RNA from formalin-fixed, paraffin-embedded (FFPE) tissue samples of the primary lesion and identifies the level of expression of the 31 genes using qRT-PCR.[3] The test also adds clinical and histologic data into the GEP values to provide an integrated prognostic assessment (i31-GEP test).

11-GEP Test

The 11-GEP test is a CM prognostic test that measures the level of expression of eight target genes and three control genes.[11] This test also measures gene expression from FFPE tissue samples after total RNA from the samples is reverse transcribed.[12] The test uses a continuous scoring system with 0 as the cut-off, such that a score ≤ 0 is considered "low-risk" for recurrence and a score > 0 is considered "high-risk" for recurrence.[12]

8-GEP + CP Test

The 8-GEP + CP test was derived from a logistic regression model consisting of eight genes and two clinicopathologic factors analyzed to predict sentinel node positivity.[13] These genes are primarily involved in epithelial-to-mesenchymal transition, angiogenesis/hypoxia, and coagulation.[13] This test dichotomizes patients into two groups: "low-risk" and "high-risk" for metastasis and relapse.

Literature Search

A comprehensive literature search of MEDLINE and Google Scholar was completed on November 3, 2022, using the keywords "cutaneous melanoma," gene expression profile", "genomics," and "prognosis" along with the Boolean term "AND" for English-language original research articles, meta-analyses, and systematic reviews published from 2019 through 2022. Articles were screened for relevance based on the description of studies that use GEP tests to assess prognosis in CM. The selected articles were then appraised by the panel and assigned a level of evidence of "level 1," "level 2," or "level 3" using the Strength of Recommendation Taxonomy (SORT) criteria.[14]

Development of Consensus Statements

A panel of six dermatologists with specialized expertise in managing CM met on December 1, 2022, to review the selected articles. Based upon their review and evaluation of the papers, formal recommendations to guide clinicians on the use of GEP tests were developed.

A modified Delphi process was used to achieve consensus among the panelists.[14] This technique employed multiple rounds of real-time voting and a required supermajority approval to adopt a recommendation. If a recommendation did not achieve supermajority acceptance, further modification through group discussion and subsequent rounds of voting occurred. The modified Delphi process has been utilized frequently to create expert recommendations within dermatology.[10, 16-18]

RESULTS

Comprehensive Literature Search

The initial literature search resulted in 785 articles that met the search criteria. After screening the articles, 32 met inclusion criteria and were distributed to the panelists for review prior to the roundtable discussion. Of these articles, the number of papers that specifically studied the validity, accuracy, or clinical utility of each test was: 22 for the 31-GEP test[4,19-24,26-31,34-42], 2 for the 11-GEP test[11,34], and 7 for the 8-GEP + CP test.[5,13,23,43-46]

Levels of Evidence Designation

The panelists assigned each of the included studies a level of evidence based on SORT criteria (**Tables 1-3**).[14] Of the 22 articles that specifically analyzed data from the 31-GEP test, 8 were deemed to represent level 1 evidence, 12 were deemed to represent level

Table 1. Strength of Recommendation Taxonomy (SORT) level of evidence for articles pertaining to the 31-GEP test.

Article	Level of Evidence
Articles reporting data on validity, accuracy, or clinical utility	
Ahmed K, Siegel JJ, Morgan-Linnell SK, et al. Attitudes of patients with cutaneous melanoma toward prognostic testing using the 31-gene expression profile test [published online ahead of print, 2022 Aug 1]. *Cancer Med*. 2022;10.1002/cam4.5047.	3
Arnot SP, Han G, Fortino J, et al. Utility of a 31-gene expression profile for predicting outcomes in patients with primary cutaneous melanoma referred for sentinel node biopsy. *Am J Surg*. 2021;221(6):1195-1199.	1
Dillon LD, McPhee M, Davidson RS, et al. Expanded evidence that the 31-gene expression profile test provides clinical utility for melanoma management in a multicenter study. *Curr Med Res Opin*. 2022;38(8):1267-1274.	2
Gastman BR, Zager JS, Messina JL, et al. Performance of a 31-gene expression profile test in cutaneous melanomas of the head and neck. *Head Neck*. 2019;41(4):871-879.	2
Glazer A, Tassavor M, Portela D, et al. (2022). The Integrated 31-Gene Expression Profile Test (i31-GEP) for Cutaneous Melanoma Outperforms the CP-GEP at Identifying Patients who can Forego Sentinel Lymph Node Biopsy when Applying NCCN Guidelines. *SKIN The Journal of Cutaneous Medicine*, *6*(6), 474–481.	2
Greenhaw BN, Covington KR, Kurley SJ, et al. Molecular risk prediction in cutaneous melanoma: A meta-analysis of the 31-gene expression profile prognostic test in 1,479 patients. *J Am Acad Dermatol*. 2020;83(3):745-753.	1
Hsueh EC, DeBloom JR, Lee JH, et al. Long-Term Outcomes in a Multicenter, Prospective Cohort Evaluating the Prognostic 31-Gene Expression Profile for Cutaneous Melanoma. *JCO Precis Oncol*. 2021;5:PO.20.00119.	1
Hyams DM, Covington KR, Johnson CE, Plasseraud KM, Cook RW. Integrating the melanoma 31-gene expression profile test with surgical oncology practice within national guideline and staging recommendations. *Future Oncol*. 2021;17(5):517-527.	2
Jarell A, Skenderis B, Dillon LD, et al. The 31-gene expression profile stratifies recurrence and metastasis risk in patients with cutaneous melanoma. *Future Oncol*. 2021;17(36):5023-5031.	2
Jarell A, Gastman BR, Dillon LD, et al. Optimizing treatment approaches for patients with cutaneous melanoma by integrating clinical and pathologic features with the 31-gene expression profile test. *J Am Acad Dermatol*. 2022;87(6):1312-1320.	2
Kangas-Dick AW, Greenbaum A, Gall V, et al. Evaluation of a Gene Expression Profiling Assay in Primary Cutaneous Melanoma. *Ann Surg Oncol*. 2021;28(8):4582-4589.	2
Keller J, Schwartz TL, Lizalek JM, et al. Prospective validation of the prognostic 31-gene expression profiling test in primary cutaneous melanoma. *Cancer Med*. 2019;8(5):2205-2212.	1
Marchetti MA, Coit DG, Dusza SW, et al. Performance of Gene Expression Profile Tests for Prognosis in Patients With Localized Cutaneous Melanoma: A Systematic Review and Meta-analysis. *JAMA Dermatol*. 2020;156(9):953-962.	1

Marchetti MA, Dusza SW, Bartlett EK. Utility of a Model for Predicting the Risk of Sentinel Lymph Node Metastasis in Patients with Cutaneous Melanoma. *JAMA Dermatol*. 2022;158(6):680-683.	2
Martin BJ, Covington KR, Quick AP, Cook RW. Risk Stratification of Patients with Stage I Cutaneous Melanoma Using 31-Gene Expression Profiling. *J Clin Aesthet Dermatol*. 2021;14(9):E61-E63.	3
Podlipnik S, Boada A, López-Estebaranz JL, et al. Using a 31-Gene Expression Profile Test to Stratify Patients with Stage I-II Cutaneous Melanoma According to Recurrence Risk: Update to a Prospective, Multicenter Study. *Cancers (Basel)*. 2022;14(4):1060.	1
Podlipnik S, Carrera C, Boada A, et al. Early outcome of a 31-gene expression profile test in 86 AJCC stage IB-II melanoma patients. A prospective multicentre cohort study. *J Eur Acad Dermatol Venereol*. 2019;33(5):857-862.	1
Thorpe RB, Covington KR, Caruso HG, et al. Development and validation of a nomogram incorporating gene expression profiling and clinical factors for accurate prediction of metastasis in patients with cutaneous melanoma following Mohs micrographic surgery. *J Am Acad Dermatol*. 2022;86(4):846-853.	2
Vetto JT, Hsueh EC, Gastman BR, et al. Guidance of sentinel lymph node biopsy decisions in patients with T1-T2 melanoma using gene expression profiling. *Future Oncol*. 2019;15(11):1207-1217.	1
Whitman ED, Koshenkov VP, Gastman BR, et al. Integrating 31-Gene Expression Profiling With Clinicopathologic Features to Optimize Cutaneous Melanoma Sentinel Lymph Node Metastasis Prediction. *JCO Precis Oncol*. 2021;5:PO.21.00162. Published 2021 Sep 13.	2
Wisco OJ, Marson JW, Litchman GH, et al. Improved cutaneous melanoma survival stratification through integration of 31-gene expression profile testing with the American Joint Committee on Cancer 8th Edition Staging. *Melanoma Res*. 2022;32(2):98-102.	2
Zakria, D., Brownstone, N., & Rigel, D. (2022). The Integrated 31-Gene Expression Profile (i31-GEP) Test for Cutaneous Melanoma Outperforms a Clinicopathologic-only Nomogram at Identifying Patients who can Forego Sentinel Lymph Node Biopsy. SKIN The Journal of Cutaneous Medicine, 6(6), 463–473.	2
Systematic Reviews or Consensus Guidelines	
Grossman D, Okwundu N, Bartlett EK, et al. Prognostic Gene Expression Profiling in Cutaneous Melanoma: Identifying the Knowledge Gaps and Assessing the Clinical Benefit. *JAMA Dermatol*. 2020;156(9):1004-1011.	3
Kwatra SG, Hines H, Semenov YR, Trotter SC, Holland E, Leachman S. A Dermatologist's Guide to Implementation of Gene Expression Profiling in the Management of Melanoma. *J Clin Aesthet Dermatol*. 2020;13(11 Suppl 1):s3-s14.	3
Litchman GH, Prado G, Teplitz RW, et al. (2020). A Systematic Review and Meta-Analysis of Gene Expression Profiling for Primary Cutaneous Melanoma Prognosis. *SKIN The Journal of Cutaneous Medicine*, *4*(3), 221–237.	1

Table 2. Strength of Recommendation Taxonomy (SORT) level of evidence for articles pertaining to the 11-GEP test.

Article	Level of Evidence
Articles reporting data on validity, accuracy, or clinical utility	
Amaral TMS, Hoffmann MC, Sinnberg T, et al. Clinical validation of a prognostic 11-gene expression profiling score in prospectively collected FFPE tissue of patients with AJCC v8 stage II cutaneous melanoma. *Eur J Cancer*. 2020;125:38-45.	1
Marchetti MA, Coit DG, Dusza SW, et al. Performance of Gene Expression Profile Tests for Prognosis in Patients With Localized Cutaneous Melanoma: A Systematic Review and Meta-analysis. *JAMA Dermatol*. 2020;156(9):953-962.	1
Systematic Reviews or Consensus Guidelines	
Grossman D, Okwundu N, Bartlett EK, et al. Prognostic Gene Expression Profiling in Cutaneous Melanoma: Identifying the Knowledge Gaps and Assessing the Clinical Benefit. *JAMA Dermatol*. 2020;156(9):1004-1011.	3
Kwatra SG, Hines H, Semenov YR, Trotter SC, Holland E, Leachman S. A Dermatologist's Guide to Implementation of Gene Expression Profiling in the Management of Melanoma. *J Clin Aesthet Dermatol*. 2020;13(11 Suppl 1):s3-s14.	3
Litchman GH, Prado G, Teplitz RW, et al. (2020). A Systematic Review and Meta-Analysis of Gene Expression Profiling for Primary Cutaneous Melanoma Prognosis. *SKIN The Journal of Cutaneous Medicine*, *4*(3), 221–237.	1

Table 3. Strength of Recommendation Taxonomy (SORT) level of evidence for articles pertaining to the 8-GEP + CP test.

Article	Level of Evidence
Articles reporting data on validity, accuracy, or clinical utility	
Bellomo D, Arias-Mejias SM, Ramana C, et al. Model Combining Tumor Molecular and Clinicopathologic Risk Factors Predicts Sentinel Lymph Node Metastasis in Primary Cutaneous Melanoma. JCO Precis Oncol. 2020;4:319-334.	3
Eggermont AMM, Bellomo D, Arias-Mejias SM, et al. Identification of stage I/IIA melanoma patients at high risk for disease relapse using a clinicopathologic and gene expression model. Eur J Cancer. 2020;140:11-18.	2
Glazer A, Tassavor M, Portela D, et al. (2022). The Integrated 31-Gene Expression Profile Test (i31-GEP) for Cutaneous Melanoma Outperforms the CP-GEP at Identifying Patients who can Forego Sentinel Lymph Node Biopsy when Applying NCCN Guidelines. *SKIN The Journal of Cutaneous Medicine*, *6*(6), 474–481.	2
Johansson I, Tempel D, Dwarkasing JT, et al. Validation of a clinicopathological and gene expression profile model to identify patients with cutaneous melanoma where sentinel lymph node biopsy is unnecessary. *Eur J Surg Oncol*. 2022;48(2):320-325.	2
Mulder EEAP, Dwarkasing JT, Tempel D, et al. Validation of a clinicopathological and gene expression profile model for sentinel lymph node metastasis in primary cutaneous melanoma. *Br J Dermatol*. 2021;184(5):944-951.	2
Mulder EEAP, Johansson I, Grünhagen DJ, et al. Using a Clinicopathologic and Gene Expression (CP-GEP) Model to Identify Stage I-II Melanoma Patients at Risk of Disease Relapse. *Cancers (Basel)*. 2022;14(12):2854.	2
Yousaf A, Tjien-Fooh FJ, Rentroia-Pacheco B, et al. Validation of CP-GEP (Merlin Assay) for predicting sentinel lymph node metastasis in primary cutaneous melanoma patients: A U.S. cohort study. *Int J Dermatol*. 2021;60(7):851-856.	2
Systematic Reviews or Consensus Guidelines	
Grossman D, Okwundu N, Bartlett EK, et al. Prognostic Gene Expression Profiling in Cutaneous Melanoma: Identifying the Knowledge Gaps and Assessing the Clinical Benefit. *JAMA Dermatol*. 2020;156(9):1004-1011.	3
Kwatra SG, Hines H, Semenov YR, Trotter SC, Holland E, Leachman S. A Dermatologist's Guide to Implementation of Gene Expression Profiling in the Management of Melanoma. *J Clin Aesthet Dermatol*. 2020;13(11 Suppl 1):s3-s14.	3
Litchman GH, Prado G, Teplitz RW, et al. (2020). A Systematic Review and Meta-Analysis of Gene Expression Profiling for Primary Cutaneous Melanoma Prognosis. *SKIN The Journal of Cutaneous Medicine*, *4*(3), 221–237.	1

2 evidence, and 2 were deemed to represent level 3 evidence. Of the two papers that analyzed data from the 11-GEP test, the panel designated both of them as level 1 evidence. Of the 7 manuscripts that analyzed data from the 8-GEP + CP test, 6 were designated as level 2 evidence and 1 was designated as level 3 evidence.

Consensus Recommendations

The panel then generated 11 consensus recommendations/statements related to indications for usage, all of which received a unanimous vote for adoption (**Table 4**). Each of the recommendations was then given a strength "A," "B,", or "C" according to SORT criteria.[14]

Usage Guidelines:

- Integrating GEP results can improve prognostic assessment for patients with T1a tumors at least 0.3mm in depth, T1b+ tumors, or any tumor in which there is significant uncertainty about adequacy of microstaging (e.g., positive deep margin) (SORT Level=A)
- GEP testing can identify a high-risk subset for recurrence, distant metastasis, or death of traditionally assessed low-risk patients (e.g., SLN negative or T1a/b) (SORT Level=A)
- GEP testing provides clinically useful information that augments risk-aligned management decisions to both rule-in or rule-out the need for SLNB and subsequent management plans (SORT Level=A)
- Adding GEP results to clinicopathologic information significantly improves CM prognosis assessment (SORT Level=B)
- Adding GEP results to AJCC classification improves prognostic assessment of cutaneous melanoma patients (SORT Level=B)
- Based on current literature, the GEP tests have not been demonstrated to show prognostic utility for *in-situ* CM and AJCC8 stage IV disease and are not indicated for those patients (SORT Level=C).

Consensus Supporting Statements:

- Current literature supports that the 31-GEP test, with its more extensive evidence-driven data, offers more utility than other existing GEP assays or nomograms (SORT Level=A)
- Integrating GEP results can increase the precision and confidence of melanoma management decisions (e.g., follow up regimens, decision for SLNB, referral to other specialties, and need for imaging) (SORT Level=B)
- Model prediction variance does impact clinical test utility (SORT Level=C).
- GEP results can be integrated into management decisions for patients being considered for adjuvant therapy (SORT Level=C).
- Based on the strength of the available literature, GEP results should be considered as a criterion for randomization and inclusion of patients to improve the validity of CM clinical trials (SORT Level=C).

DISCUSSION

GEP testing has become an accepted clinical tool to aid in the prognostic assessment of numerous malignancies, including skin, breast, lung, colorectal, and prostate cancer.[3] Its use in CM is already commonplace, with data from over 1,000 31-GEP CM tests in the US currently being integrated into patient management decisions every month.[25]

Table 4. Consensus statements and recommendations for incorporating GEP testing into clinical practice and their corresponding strength using SORT criteria.

Recommendation	Strength of Recommendation	Consensus Vote
Usage Guidelines		
Integrating GEP results can improve prognostic assessment for patients with T1a tumors at least 0.3mm in depth, T1b+ tumors, or any tumor in which there is significant uncertainty about adequacy of microstaging (e.g., positive deep margin)	A	6/6
GEP testing can identify a high-risk subset for recurrence, distant metastasis, or death of traditionally assessed low-risk patients (e.g., SLN negative or T1a/b)	A	6/6
GEP testing provides clinically useful information that augments risk-aligned management decisions to both rule-in or rule-out the need for SLNBx and subsequent management plans	A	6/6
Adding GEP results to clinicopathologic information significantly improves CM prognosis assessment	B	6/6
Adding GEP results to AJCC classification improves prognostic assessment of cutaneous melanoma patients	B	6/6
Based on current literature, the GEP tests have not been demonstrated to show prognostic utility for *in-situ* CM and AJCC8 stage IV disease	C	6/6
Consensus Supporting Statements		
Current literature supports that the 31-GEP test, with its more extensive evidence-driven data, offers more utility than other GEP assays or nomograms	A	6/6
Integrating GEP results can increase the precision and confidence in melanoma management decisions (e.g., follow up regimens, referral to other specialties, and need for imaging)	B	6/6
Model prediction variance does impact clinical test utility.	C	6/6
GEP results can be integrated into management decisions for patients being considered for adjuvant therapy	C	6/6
Based on the strength of the available literature, GEP results should be considered as a criterion for randomization and inclusion of patients to improve the validity of CM clinical trials	C	6/6

Despite multiple validation and clinical utility studies in the literature, there remains a lack of integration of GEP testing into some of the formal models and guidelines for CM management. The AJCC8 prognostic model only uses Breslow depth, ulceration status, and sentinel node positivity to distinguish between stage I-III CM and does not mention a tumor's genetic profile.[47] Furthermore, routine GEP testing is not currently incorporated into NCCN[48] or AAD[49] CM management recommendations.

GEP tests are important tools as they can provide substantial prognostic information. The EXPAND and INTEGRATE trials were two multi-center prospective clinical studies that demonstrated that the 31-GEP test is able to further stratify patients beyond AJCC8 staging in patients with stage I-III CM.[26] These studies found that patients with a 31-GEP class 2 result had significantly lower 3-year recurrence free survival (RFS) than those with a class 1 result (83% vs 97%, $p < 0.0001$).[26] Additionally, CMs with a class 2 result had lower distant metastasis free survival (DMFS) (87% vs 99%, $p < 0.0001$) and overall survival (OS) (90% vs 98%, $p = 0.01$) compared to those with a class 1 result.[26] A retrospective validation study of the 11-GEP test in stage II CM showed that patients with a high GEP score (GEPS) had a significantly lower 5-year melanoma-specific survival (MSS) and 10-year MSS compared to patients with a low GEPS (82% vs 92% and 67% vs 92%, $p = 0.018$).[11] Furthermore, in a multi-center retrospective cohort study with 837 patients, the 8-GEP + CP test identified a high-risk patient group (47% of total stage I/IIA patients) that had a much worse five-year RFS than the low-risk patient group (74% vs 89%; HR = 2.98; $p<0.0001$).[5]

The information provided by these tests can also further guide clinical management plans, such as the decision to perform a sentinel lymph node biopsy (SLNB). According to NCCN guidelines, SLNB is not recommended for patients with a < 5% chance of a positive node, should be discussed and considered for patients with a 5-10% chance of a positive node, and should be discussed and offered to patients with a > 10% chance of SLN positivity.[48] While sentinel lymph node positivity is a key prognostic marker, studies have shown that < 20% of patients who undergo the biopsy are found to have nodal metastasis.[50] Given that the procedure has a > 10% risk of complications such as bleeding, infection, pain, neuropathy, lymphocele, lymphatic fistula, and lymphedema[4], identifying patients that can safely forego the biopsy can significantly reduce morbidity. A multi-center validation study of the i-31 GEP test (a test that integrates the 31-GEP with clinicopathological features including Breslow thickness, mitotic rate, ulceration status, and patient age) showed that the test increased the proportion of patients with T1-T4 tumors predicted to have <5% risk of SLNB positivity from 8.5% to 27.7% with a negative predictive value (NPV) of 98%.[41] Moreover, for patients with T1 tumors originally classified to have a likelihood of SLNB positivity of 5-10%, the i31-GEP was able to reclassify 63% of these cases as either having < 5% or >10% risk of positive SLNB[41], a valuable distinction to help guide the decision of whether or not the procedure is necessary. For the 8-GEP + CEP test, a validation study analyzing the test's ability to predict SLNB positivity found that this model has a NPV of 90.5% (95% Confidence Interval [CI]: 77.9-96.2%) in T1-4 CMs.[44]

In comparing the three GEP tests, the panel consensus was that there were significantly more studies supporting the validity, accuracy, and clinical utility of the 31-GEP test compared to the 11-GEP and 8-GEP +

CP tests (22 studies validating the 31-GEP test[4,19-24,26-31,34-42], compared to just 2 studies validating the 11-GEP test[11,34] and 7 studies validating the 8-GEP + CP test[5,13,23,43-46]). Based on the limited studies for the 8-GEP + CP and the 11-GEP test, the panel concluded that there was insufficient data to assess their validity and utility or currently recommend usage in the clinical setting until further studies are performed.

Within the reviewed set of papers, there were studies showing head-to-head superiority of the 31-GEP test over other tests. A retrospective comparison of the i31-GEP test and the 8-GEP + CP test showed that the i-31GEP had a 30:1 true-to-false-negative SLNB ratio compared to a 15:1 ratio for the 8-GEP + CP test.[23] Another study found that the i31-GEP test was able to outperform an online nomogram from the Melanoma Institute of Australia (MIA)[51] given the wide variance of that model's prediction,[4] which may not be actionable within NCCN guideline parameters. In comparing this nomogram with the i31-GEP in a retrospective cohort of 582 patients, the i-31GEP was able to identify 28.5% of patients as having a <5% risk of SLNB positivity while also having an upper 95% CI ≤ 10% compared with only a 0.9% ($p<0.001$) when using the MIA nomogram.[4] Furthermore, for patients with a pre-test probability of SLNB positivity between 5-10%, the i-31GEP reclassified 60.2% (171/284) of cases as representing < 5% or > 10% risk compared to 13.7% (39/284, $p<0.001$) using the MIA nomogram.[4]

This panel review has several limitations. The recommendations created by the panel did not take into account the cost of these tests or their impact on healthcare spending, but some studies have shown cost-effectiveness of GEP tests.[40,52] Also, this panel consensus was designed to provide an update from a prior expert consensus[10] that reviewed the available literature existent at that time. This current consensus is based specifically upon articles that were published subsequent to that article.

CONCLUSION

CM represents a significant public health concern, as it has a rising incidence and material mortality rate despite advances in diagnosis and therapy. Additional tools to aid in prognostic assessment and risk-aligned management decisions have the potential to significantly reduce morbidity, mortality, and healthcare costs. Significant peer-reviewed literature exists supporting the incorporation of genomics into CM clinical assessment and management. The expert consensus guidelines and support statements presented here will hopefully provide a framework for the clinician to integrate GEP testing into their CM patient management.

The recommendations created by this Expert Consensus Panel have been adopted as an official policy recommendation by the National Society for Cutaneous Medicine.

Conflict of Interest Disclosures: DZ, NB, DS and GL, and GG have no conflicts. BB is a consultant to Castle Biosciences, Inc., LEO Pharma, and Sun Pharma. RC has served on advisory boards for Castle Biosciences. ML is an employee of Mount Sinai and receives research funds from: Abbvie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Cara therapeutics, Dermavant Sciences, Eli Lilly, Incyte, Janssen Research & Development, LLC, Ortho Dermatologics, Regeneron, and UCB, Inc., and is a consultant for Aditum Bio, Almirall, AltruBio Inc., AnaptysBio, Arcutis, Inc., Arena Pharmaceuticals, Aristea Therapeutics, Avotres Therapeutics, BiomX, Brickell Biotech, Boehringer-Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Castle Biosciences, Celltrion, Corevitas, Dermavant Sciences, Evommune, Inc., Facilitatation of International Dermatology Education, Forte Biosciences, Foundation for Research and Education in Dermatology, Hexima Ltd., LEO Pharma, Meiji Seika

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