

## Review

# 31-Gene expression profiling for cutaneous melanoma: an expert consensus panel

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**Keywords:** 31-gene expression profiling, clinical utility, melanoma, prognosis, risk stratification, sentinel lymph node biopsy

## Dermatology Online Journal

Vol. 31, Issue 5, 2025

### Abstract

#### Purpose

To review published literature on the clinical efficacy, use, and accuracy of the 31-gene expression profiling (31-GEP) test for prognostic information in invasive melanoma.

#### Methods

A comprehensive literature search used keywords "31-gene expression profiling," "melanoma," "prognosis," "clinical efficacy," and "clinical utility." A panel of 10 dermatologists with expertise in melanoma management reviewed the articles and created consensus statements. A modified Delphi process approved each statement, requiring supermajority approval through multiple rounds of real-time voting, with strength of recommendation assigned.

#### Results

The search produced 150 articles; 26 met inclusion criteria. The panel unanimously voted to adopt 9 consensus statements and recommendations regarding 31-GEP testing: 8 with strength "A" and 1 with strength "C."

#### Conclusion

The panel agreed there is strong support for using 31-GEP testing to provide prognostic information for invasive melanoma. The test provides

prognostic information when thickness and other traditional factors are unknown, improves prognosis assessment when added to American Joint Committee on Cancer 8th edition staging system, and is associated with improved melanoma-specific mortality and overall survival. The panel concluded that the robust existing literature strongly supports its use as a best practice for appropriate patients with melanoma.

## Introduction

Cutaneous melanoma is among the most prevalent malignancies in the United States.<sup>1</sup> Traditional prognostication primarily relies on the American Joint Committee on Cancer 8th edition (AJCC8) staging system, which incorporates defined clinicopathologic parameters to stratify risk.<sup>2</sup> The National Comprehensive Cancer Network (NCCN) guidelines further classify patients into low-risk (stage I-IIA) and high-risk (stage IIB-III), with recommendations for more intensive care for high-risk patients.<sup>3</sup> These systems have their limitations, however, as they do not provide individualized prognosis profiles, and literature has demonstrated heterogeneous survival rates for patients within each AJCC8 stage and NCCN risk category (ie, early-stage melanoma can be high-risk for disease progression).<sup>3,4</sup>

The 31-gene expression profiling (31-GEP) prognostic test was developed to assess the expression of specific gene targets to evaluate the risk of melanoma metas-

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tasis.<sup>5,6</sup> It classifies patients as: low risk (Class 1A), intermediate risk (Class 1B/2A), or high risk (Class 2B) for melanoma recurrence, metastasis, and melanoma-specific survival (MSS).<sup>7-9</sup> The 31-GEP test has been validated as an independent predictor of regional or distant metastatic recurrence and death, and has been used by clinicians to inform decisions for obtaining sentinel lymph node (SLN) biopsy.<sup>5,6,10,11</sup> Using 31-GEP test results with traditional staging methods can enhance assessment of patient's prognosis, and clinicians have demonstrated its use in altering management guidance.<sup>12,13</sup> The integrated 31-GEP (i31-GEP) result further combines 31-GEP testing with clinicopathologic (CP) features to provide a personalized risk assessment for SLN positivity in patients with invasive melanoma.<sup>10</sup> Despite the published data, there is a lack of clarity regarding how and when the test should be used in everyday clinical practice.

Herein, we review the published literature on the clinical efficacy, use, and accuracy of the prognostic 31-GEP test to guide real-world, data-informed clinical decision-making and enhance patient care.

## Methods

### Literature Search and Study Selection

A comprehensive literature search of PubMed, Scopus, and Google Scholar was conducted on April 5, 2025, using a combination of keywords: "31-gene expression profiling," "melanoma," "prognosis," "clinical efficacy," and "clinical utility," along with the Boolean term "AND," for English-language original research articles, systematic reviews, and meta-analyses without date restrictions. This study did not require institutional review board approval. Articles were screened for relevance to 31-GEP testing for prognostic information in invasive melanoma. Ten board-certified dermatologists with expertise in melanoma management were asked to participate in a panel. Articles that met inclusion criteria were distributed to the panelists, and each member was assigned a level of evidence based on Strength of Recommendation Taxonomy (SORT) criteria.<sup>14</sup> Levels include level 1 (good-quality, patient-oriented evidence), level 2 (limited-quality, patient-oriented evidence), and level 3 (other).<sup>14</sup>

### Development of Consensus Statements

The panel convened on April 16, 2025, to discuss the studies and create consensus statements. A modified Delphi process was used to reach consensus for each statement, which requires two-thirds supermajority approval for adoption of a recommendation. If a statement does not receive supermajority approval, it undergoes multiple rounds of real-time modification and voting until two-thirds supermajority is reached.<sup>15-17</sup> Consensus statements were assigned a strength of recommendation of A (consistent, good-quality, patient-oriented evi-

dence), B (inconsistent, limited-quality, patient-oriented evidence, or C (consensus, opinion).

## Results

### Literature Search and Study Selection

The literature search identified 150 articles that met search criteria. After a comprehensive screening process, 26 articles were selected as relevant to the research questions ([Figure 1](#)).

### Levels of Evidence Designation

For the 26 evaluated articles, the panel assigned level 1 evidence to 9 articles, level 2 evidence to 13 articles, and level 3 evidence to 4 articles ([Table 1](#)).

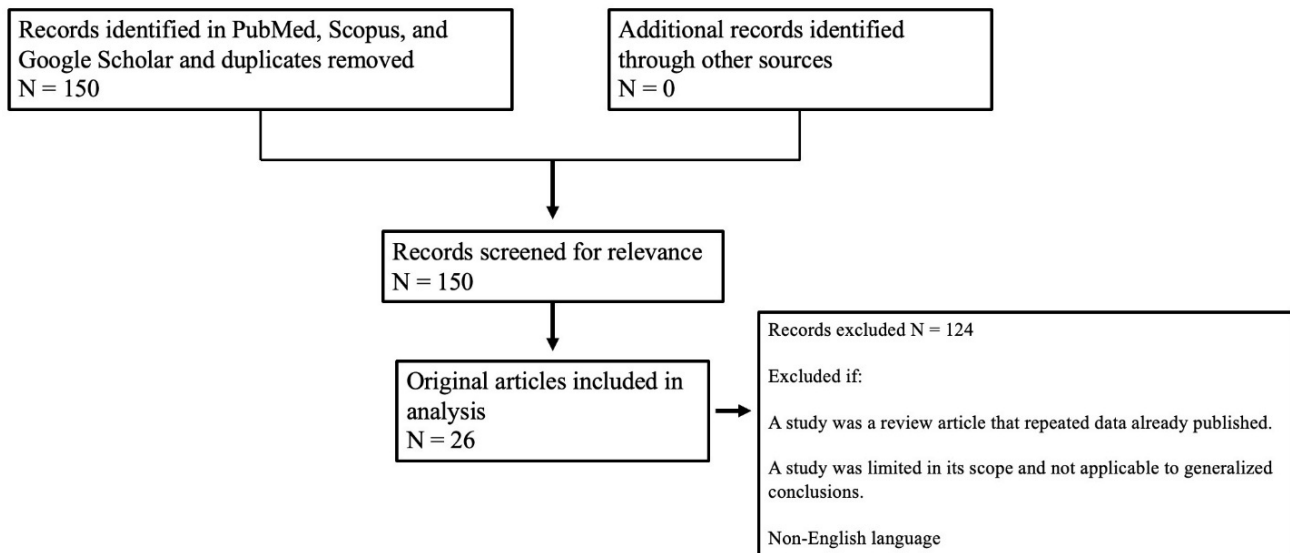
### Consensus Statements

The panel developed 9 consensus statements. All 9 statements received a unanimous (10/10) vote for adoption. Each statement was assigned a strength based on SORT criteria ([Table 2](#)).

*Statement 1: Multiple studies (including prospective studies) have demonstrated clinical efficacy for the 31-GEP test in providing consistent and accurate prognostic information for invasive melanoma (SORT Level A, 10/10 approved).*

The clinical efficacy of 31-GEP testing has been demonstrated across numerous studies. A recent meta-analysis of 13 studies including 14,760 patients found that the 31-GEP test consistently stratified patients into risk groups.<sup>18</sup> Five-year melanoma-specific survival rates were 99.8% for 31-GEP Class 1A, 97.6% for Class 1B/2A, and 83.4% for Class 2B.<sup>18</sup> Recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) rates demonstrated similar patterns.<sup>18</sup> Another meta-analysis including 1479 patients found that Class 1A patients had a 5-year RFS rate of 91.4% and a DMFS rate of 94.1%, while Class 2B patients had a 5-year RFS rate of 43.6% and a DMFS rate of 55.5% ( $P < .0001$ ).<sup>19</sup> The 31-GEP test also identified AJCC8 stage I-III patients with high likelihood for recurrence and distant metastasis (76% sensitivity for both).<sup>19</sup> Sensitivity was 77.8% with a negative predictive value (NPV) of 95%, indicating that patients with a low-risk 31-GEP result may safely undergo less intensive treatment without increased risk of adverse events.<sup>20</sup>

In 2 multicenter registry studies including 323 patients with stage I-III melanoma, the 31-GEP test was a significant predictor of RFS, DMFS, and overall survival (OS).<sup>21</sup> Patients classified as Class 2 on the 31-GEP test had a significantly lower 3-year RFS, DMFS, and OS.<sup>21</sup> Other studies have also found that the 31-GEP test is an independent predictor of recurrence and distant metastasis,<sup>7,19,20,22,23</sup> and has superior accuracy compared with SLN biopsy.<sup>22</sup> One study linked patients with stage I-III melanoma who underwent 31-GEP testing to National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program registries.<sup>24</sup> The 31-GEP test accurately stratified patients according to their MSS; patients



**Figure 1.** Comprehensive review of 31-GEP testing. Studies were deemed eligible if they were published in English and examined the clinical efficacy and use of the 31-GEP test, as well as its role in assessing prognosis of invasive melanoma compared with traditional staging methods and other available nomograms. Studies not written in English, review articles repeating previously published material, and studies limited in scope or not generalizable were excluded.

with a Class 1A result had a higher 3-year MSS and OS compared with those with Class 1B/2A or Class 2B results.<sup>24</sup> With extended follow-up periods of up to 4 years, a Class 2B significantly predicted 3-year disease-free survival and effectively stratified patients by relapse risk.<sup>20</sup>

*Statement 2: Studies have shown clinical utility for the 31-GEP test for providing prognostic information for invasive melanoma (SORT Level A, 10/10 approved).*

The 31-GEP test has the capacity to deliver robust prognostic information that can effectively inform clinical decision-making and patient management strategies.<sup>16, 25-27</sup> The test can identify low-risk patients who are classified into higher-risk stages and vice versa, which can alter management decisions. One study reported that after receiving 31-GEP results, 50.6% of patients experienced a change in management plans.<sup>13</sup> These changes, including clinic visits, lab work, or surveillance imaging, were associated with the risk estimated by the 31-GEP test for 76.1% of Class 1 patients and 78.7% of Class 2 patients.<sup>13</sup> A prospective study evaluating the prognostic utility of the 31-GEP test found that Class 2 result was independently associated with recurrence and distant metastasis in primary melanoma patients.<sup>28</sup> In another study, management plans changed for 49% of patients compared to pre-test recommendations after knowledge of the 31-GEP test result, where 36% of Class 1 patients and 85% of Class 2 patients had a modification in management.<sup>26</sup> Additionally, another study found that 47% of patients with melanoma stage I/IIA were classified as high-risk based on 31-GEP testing, with a significantly worse 5-year RFS compared with the low-risk group (74% versus 89%;  $P < .0001$ ).<sup>29</sup>

Based on published literature, multiple expert consensus panels recommended that the 31-GEP test can make

significant improvements in clinical decision-making for management of melanoma (SORT level A).<sup>16,30</sup>

*Statement 3: Studies have shown clinical efficacy for the 31-GEP test in providing prognostic information for invasive melanoma when the thickness or other traditional factors are unknown (SORT Level A, 10/10 approved).*

Variability occurs commonly in the CP information available for patients diagnosed with invasive melanoma. This may alter staging assessment and clinical management. Owing to discrepancies in biopsies and restrictions that may arise with cosmetically sensitive (eg, head and neck) or anatomically restrictive (eg, acral skin) areas, pigmented lesions that are diagnosed as melanoma may have unknown thickness, ulceration, microsatellites, or other traditional factors. One study found that of 714 patients, 24% had transected melanomas,<sup>31</sup> while another study reported that of 1129 patients, 39% had positive deep margin on original biopsy.<sup>32</sup>

Whitman et al<sup>10</sup> described how the i31-GEP combines the 31-GEP test with CP features by using an artificial intelligence-based neural network algorithm and thereby predicts a risk of SLN positivity in patients with T1-T4 invasive melanoma. This study included patients with melanomas transected at the base and those that lack other traditional factors, grouping them as high-risk T1a.<sup>10</sup> The i31-GEP test reclassified 68.5% of high-risk T1a tumors and 40.9% of T1b tumors as having less than 5% risk of positive SLN biopsy.<sup>10</sup> Overall, the i31-GEP expanded the proportion of patients with T1-T4 tumors identified as having less than 5% probability of SLN biopsy positivity from 8.5% to 27.7%, reporting an NPV of 98%.<sup>10</sup> Another study showed that combining 31-GEP with CP factors can provide patients with personalized risk of recurrence (ROR) or death.<sup>8</sup> Patients with a low-risk i31-ROR test result were found to have a significantly

**Table 1.** Strength of Recommendation Taxonomy Criteria Level of Evidence for Articles.

Article	Level of Evidence
Ahmed K, Siegel JJ, Morgan-Linnell SK, LiPira K. Attitudes of patients with cutaneous melanoma toward prognostic testing using the 31-gene expression profile test. <i>Cancer Med.</i> 2023;12(2):2008-2015.	3
Arnot SP, Han G, Fortino J, Han D, Fowler G, Vetto JT. Utility of a 31-gene expression profile for predicting outcomes in patients with primary cutaneous melanoma referred for sentinel node biopsy. <i>Am J Surg.</i> 2021;221(6):1195-1199.	1
Bailey CN, Martin BJ, Petkov VI, et al. 31-Gene Expression Profile Testing in Cutaneous Melanoma and Survival Outcomes in a Population-Based Analysis: A SEER Collaboration. <i>JCO Precis Oncol.</i> 2023;7:e2300044.	2
Burshtein J, Zakria D, Shah M, et al. Advances in Technology for Melanoma Diagnosis and Prognosis: An Expert Consensus Panel. <i>J Drugs Dermatol.</i> 2024;23(9):774-781.	3
Dhillon S, Duarte-Bateman D, Fowler G, et al. Routine imaging guided by a 31-gene expression profile assay results in earlier detection of melanoma with decreased metastatic tumor burden compared to patients without surveillance imaging studies. <i>Arch Dermatol Res.</i> 2023 Oct;315(8):2303.	2
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. <i>Curr Med Res Opin.</i> 2022;38(8):1267-1274.	2
Durgham RA, Nassar SI, Gun R, Nguyen SA, Asarkar AA, Nathan CO. The Prognostic Value of the 31-Gene Expression Profile Test in Cutaneous Melanoma: A Systematic Review and Meta-Analysis. <i>Cancers (Basel).</i> 2024;16(21):3714.	1
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. <i>Eur J Cancer.</i> 2020;140:11-18.	2
Gastman BR, Gerami P, Kurley SJ, Cook RW, Leachman S, Vetto JT. Identification of patients at risk of metastasis using a prognostic 31-gene expression profile in subpopulations of melanoma patients with favorable outcomes by standard criteria. <i>J Am Acad Dermatol.</i> 2019;80(1):149-157.e4.	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. <i>J Am Acad Dermatol.</i> 2020;83(3):745-753.	1
Guenther JM, Ward A, Martin BJ, et al. A Prospective, Multicenter Analysis of Recurrence-Free Survival After Sentinel Lymph Node Biopsy Decisions Influenced by the 31-GEP. <i>Cancer Med.</i> 2025;14(7):e70839.	1
Guenther JM, Ward A, Martin BJ, et al. A prospective, multicenter analysis of the integrated 31-gene expression profile test for sentinel lymph node biopsy (i31-GEP for SLNB) test demonstrates reduced number of unnecessary SLNBs in patients with cutaneous melanoma. <i>World J Surg Oncol.</i> 2025;23(1):5.	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. <i>JCO Precis Oncol.</i> 2021;5:PO.20.00119.	2
Jarell A, Skenderis B, Dillon LD, et al. The 31-gene expression profile stratifies recurrence and metastasis risk in patients with cutaneous melanoma. <i>Future Oncol.</i> 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. <i>J Am Acad Dermatol.</i> 2022;87(6):1312-1320.	2
Keller J, Schwartz TL, Lizalek JM, et al. Prospective validation of the prognostic 31-gene expression profiling test in primary cutaneous melanoma. <i>Cancer Med.</i> 2019;8(5):2205-2212.	1
Kriza C, Martin B, Bailey CN, Bennett J. Integrating the melanoma 31-gene expression profile test with clinical and pathologic features can provide personalized precision estimates for sentinel lymph node positivity: an independent performance cohort. <i>World J Surg Oncol.</i> 2024;22(1):228.	2
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. <i>J Eur Acad Dermatol Venereol.</i> 2019;33(5):857-862.	1
Podlipnik S, Boada A, López-Estebarez 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. <i>Cancers (Basel).</i> 2022;14(4):1060.	1
Podlipnik S, Martin BJ, Morgan-Linnell SK, et al. The 31-Gene Expression Profile Test Outperforms AJCC in Stratifying Risk of Recurrence in Patients with Stage I Cutaneous Melanoma. <i>Cancers (Basel).</i> 2024;16(2):287.	2
Thorpe RB, Covington KR, Caruso HG, et al. Development and validation of a nomogram incorporating gene	1

Article	Level of Evidence
expression profiling and clinical factors for accurate prediction of metastasis in patients with cutaneous melanoma following Mohs micrographic surgery. <i>J Am Acad Dermatol.</i> 2022;86(4):846-853.	
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. <i>JCO Precis Oncol.</i> 2021;5:PO.21.00162. Published 2021 Sep 13. doi:10.1200/PO.21.00162	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. <i>Melanoma Res.</i> 2022;32(2):98-102.	2
Yamamoto M, Sickel-Santanello B, Beard T, et al. The 31-gene expression profile test informs sentinel lymph node biopsy decisions in patients with cutaneous melanoma: results of a prospective, multicenter study. <i>Curr Med Res Opin.</i> 2023;39(3):417-423.	3
Zakria, D., Brownstone, N., Rigel, D. 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. <i>SKIN J Cutan Med.</i> 2022;6:463-473.	2
Zakria D, Brownstone N, Berman B, et al. Incorporating Prognostic Gene Expression Profile Assays into the Management of Cutaneous Melanoma: An Expert Consensus Panel. <i>SKIN J Cutan Med.</i> 2023;7(1):556-569. doi:10.25251/skin.7.1.1	3

**Table 2.** Consensus Statements.

Consensus Statements	Strength of Recommendation	Consensus Vote
Statement 1: Multiple studies (including prospective studies) have demonstrated clinical efficacy for the 31-GEP test in providing consistent and accurate prognostic information for invasive melanoma.	A	10/10
Statement 2: Studies have shown clinical utility for the 31-GEP test for providing prognostic information for invasive melanoma.	A	10/10
Statement 3: Studies have shown clinical efficacy for the 31-GEP test in providing prognostic information for invasive melanoma when the thickness or other traditional factors are unknown.	A	10/10
Statement 4: Integration of 31-GEP testing with traditional staging methods can accurately inform the decision to recommend sentinel lymph node biopsy.	A	10/10
Statement 5: There is a statistically significant improvement in assessing prognosis when adding 31-GEP results to AJCC8 staging.	A	10/10
Statement 6: 31-GEP testing is more accurate and precise than online nomograms in predicting the need for sentinel lymph node biopsy.	A	10/10
Statement 7: Patients who have received 31-GEP testing have improved MSS and OS in comparison to patients who have not received 31-GEP testing.	A	10/10
Statement 8: Limited data suggest that patients are more likely than not to be receptive to receiving the data from the 31-GEP test in the discussion about their invasive melanoma and management.	C	10/10
Statement 9: The existing data strongly support the utilization of 31-GEP testing as a best practice for the appropriate melanoma patient.	A	10/10

greater 5-year RFS, DMFS, and MSS compared to a high-risk i31-ROR result ( $P < .001$ ).

*Statement 4: Integration of 31-GEP testing with traditional staging methods can accurately inform the decision to recommend sentinel lymph node biopsy (SORT Level A, 10/10 approved).*

A prospective study reported that the 31-GEP test influenced 85.3% of clinical decisions related to SLN biopsy,

and 52.4% of clinical decisions were to forego SLN biopsy.<sup>11</sup> This study also demonstrated a clinically meaningful reduction of SLN biopsies by 29.4% for those with Class 1A melanoma versus a baseline of 78.0% ( $P < .01$ ).<sup>11</sup> For those aged 55 years and older and 65 years and older, SLN biopsy was reduced by 32.3% and 28.3%, respectively ( $P < .01$ ).<sup>11</sup> Another analysis revealed that patients classified as 31-GEP test Class 1A exhibited lower

SLN biopsy positivity rates and higher MSS compared to those with Class 2B results, further supporting the test's capability to identify patients who may safely avoid SLN biopsy.<sup>33</sup>

A recent prospective, multicenter analysis assessed the accuracy of the i31-GEP test for SLN biopsy risk prediction in patients with T1-T2 tumors.<sup>34</sup> This study found that there were no patients with less than 5% i31-GEP predicted risk who had a positive SLN biopsy, and there was a reported 18.5% reduction in number of SLN biopsies.<sup>34</sup> Using the i31-GEP test, the number of unnecessary SLN biopsies could have been reduced by 19% for all patients and 25% to 33% for those with T1-T2 tumors.<sup>34</sup> Of the patients with a 31-GEP Class 1A result from the same prospective study, 48% had SLN biopsy, and of those, 3.2% had a positive biopsy.<sup>36</sup> There were no recurrences in patients with a Class 1A result after a 2-year median follow-up period, demonstrating that the 31-GEP test can recognize patients who have a low risk of SLN positivity and recurrence.<sup>36</sup> Another study further supported the use of the i31-GEP test in identifying patients who could safely forego SLN biopsy (less than 5% risk of SLN biopsy positivity).<sup>35</sup> Those considered low-risk based on the i31-GEP test had a significantly lower rate of SLN biopsy positivity compared with those with greater than 10% risk (0% versus 31.9%;  $P < .001$ ).<sup>35</sup>

*Statement 5: There is a statistically significant improvement in assessing prognosis when adding 31-GEP results to AJCC8 staging (SORT Level A, 10/10 approved).*

A retrospective, multicenter study assessed whether the 31-GEP test can additionally stratify MSS within each AJCC8 stage.<sup>12</sup> This study found that overall 5-year MSS was similar to AJCC8 for each stage I, II, and III, but in the combined stage I-III cohort, the addition of 31-GEP results significantly stratified MSS ( $P < .001$ ).<sup>12</sup> Class 1A patients had a higher 5-year MSS compared with Class 2B patients (98.7% versus 77.8%).<sup>12</sup> Additionally, within the AJCC8 stage I group, those identified as Class 1A had a significantly higher 5-year MSS compared to Class 2B (99.7% versus 92.8%).<sup>12</sup> The results for stage II and stage III groups were similar to stage I, as 31-GEP Class 1A had a significantly higher 5-year MSS compared to Class 2B for each.<sup>12</sup> Cox regression analysis showed that the 31-GEP status was a significant predictor of melanoma-specific mortality, in addition to positive SLN and Breslow thickness.<sup>12</sup> Therefore, incorporating 31-GEP results with AJCC8 staging has the potential to improve MSS stratification.

Another study similarly found that the 31-GEP test improves identification of high-risk melanoma when combined with the AJCC8 online prediction tool.<sup>37</sup> Also, multivariate regression comparing 31-GEP results with AJCC8 tools found the 31-GEP test had a significantly greater prediction of distant metastasis and death compared to AJCC8 predicted risk.<sup>37</sup> Additionally, the 31-GEP test has been incorporated into a nomogram with clinical and pathologic data (Breslow depth, ulceration, mitotic rate, SLN status) to enhance prognostic accuracy.<sup>38</sup> This nomogram was found to more accurately predict the risk

of metastasis compared with the 31-GEP test or T-stage alone.<sup>38</sup>

Additionally, a large, multicenter registry study found that combining 31-GEP results with AJCC8 staging improved sensitivity of 3-year RFS (76%), DMFS (88%), and OS (76%) compared to each alone (AJCC8 alone: RFS, 57%; DMFS, 62%; OS, 60%; 31-GEP alone: RFS, 64%; DMFS, 69%; OS, 68%).<sup>21</sup> Similar to other studies, 31-GEP Class 2 results identified patients with AJCC8 stage I-IIA with an increased risk of recurrence, distant metastasis, and death and 31-GEP Class 1 results identified patients with low risk of each.<sup>21</sup>

*Statement 6: 31-GEP testing is more accurate and precise than online nomograms in predicting the need for sentinel lymph node biopsy (SORT Level A, 10/10 approved).*

The 31-GEP test has been shown to have accuracy and precision in predicting the need for SLN biopsy. Online nomograms have also been developed to identify patients at low or high risk of SLN positivity by incorporating clinical and pathological features. One such nomogram was published by the Melanoma Institute of Australia (MIA).<sup>39</sup> Several limitations of this nomogram have been described. One such limitation is the broad range of the 95% confidence intervals for SLN positivity prediction, with 1 case demonstrating 0% to 20% range leading to equivocal recommendations.<sup>40</sup> Other limitations include discordances on particular tumor subtyping and variability in reporting of lymphovascular invasion, which affects risk predictions especially with thin tumors.<sup>40</sup> One study found that the i31-GEP test identified significantly more patients with T1-T2 tumors as having less than 5% risk of SLN positivity compared with the MIA nomogram (28.5% versus 0.9%;  $P < .001$ ).<sup>41</sup> For tumors falling into the 5% to 10% pre-test likelihood of SLN positivity, the i31-GEP test also reclassified a significantly higher number as being less than 5% or greater than 10% risk versus the MIA nomogram (60.2% versus 13.7%;  $P < .001$ ).<sup>41</sup> Further, the i31-GEP test was shown to have greater precision, as it produces a continuous risk score while the MIA nomogram reports whole integers.<sup>41</sup> Another study demonstrated that the i31-GEP test outperforms a nomogram published by Memorial Sloan Kettering Cancer Center (MSKCC).<sup>42</sup> In patients who had a less than 5% predicted risk, SLN positivity was significantly lower for i31-GEP compared with MSKCC (2.7% versus 10.0%;  $P = .026$ ).<sup>42</sup>

In addition, an analysis of the MIA nomogram demonstrated net harm at a risk threshold of 5% to 8% and 10%; the MSKCC nomogram had net harm at 6% to 8%.<sup>43</sup> Based on the MIA nomogram, out of 100 patients, the number of interventions able to be avoided without missing a biopsy for a patient with a positive SLN was 0 at both 5% to 8% and 10% risk thresholds.<sup>43</sup> Another recently published analysis found similar results for both the MIA and MSKCC nomograms, with the greatest benefit seen for T2 melanomas using a threshold of 10%.<sup>44</sup>

*Statement 7: Patients who have received 31-GEP testing have improved MSS and OS in comparison to patients who have not received 31-GEP testing (SORT Level A, 10/10 approved).*

There is improved survival (MSS and OS) in patients who have received 31-GEP testing. One study linked data from SEER registries to 31-GEP testing results and compared survival outcomes in patients who received 31-GEP testing with those who did not.<sup>24</sup> Cohorts were matched so that there were no differences for any propensity score-matched variables.<sup>24</sup> Patients who received 31-GEP testing experienced a 29% lower MSS mortality (hazard ratio [HR], 0.71) in addition to a 17% lower overall mortality (HR, 0.83) versus those who did not have 31-GEP testing.<sup>24</sup> When the matching procedure was performed for 1000 iterations to reproduce the result, 31-GEP testing was associated with a median HR of 0.74 for MSS and HR 0.83 for OS.<sup>24</sup>

Although existing literature supports the efficacy of 31-GEP testing in enhancing melanoma survival outcomes, the methodologies used do not definitively elucidate the underlying mechanisms responsible for these observed improvements. The expert panel believes superior survival could result from a change in management by clinicians. These actions could be increased surveillance and clinical monitoring, more frequent imaging, and decision-making regarding whether to pursue SLN biopsy. Studies have shown that the results from the 31-GEP test alters management with changes to lower- and higher-intensity recommendations based on the result.<sup>13</sup>

*Statement 8: Limited data suggest that patients are more likely than not to be receptive to receiving the data from the 31-GEP test in the discussion about their invasive melanoma and management (SORT Level C, 10/10 approved).*

Most patients who have been diagnosed with cancer desire information regarding their prognosis and rate prognostic information as one of the most important components of communication.<sup>45-47</sup> The significance of shared decision-making between patients and providers is increasingly emphasized, highlighting the need for clinicians to effectively communicate information that enables patients to weigh the risks and benefits of different management options.<sup>48</sup> Ahmed et al<sup>49</sup> administered a survey to melanoma patients about their feelings regarding 31-GEP testing. Of the 108 respondents (28 received 31-GEP testing), 90% preferred knowing prognostic information upon diagnosis.<sup>49</sup> Furthermore, of those who received 31-GEP testing, 92% felt the results were useful and their regret scores were significantly lower compared with neutral, regardless of the 31-GEP test result.<sup>49</sup> Interestingly, there was no significant difference in regret scores between those who had a 31-GEP Class 1 result and a Class 2 result, revealing that patients felt the information provided by this prognostic testing was beneficial for them, and they were not regretful about their decision to obtain the test.<sup>49</sup> Although preliminary studies have demonstrated favorable patient responses to 31-GEP testing, there remains a need for additional patient-centered data to better understand its impact on prognostic communication and decision-making in melanoma care.

*Statement 9: The existing data strongly support the utilization of 31-GEP testing as a best practice for the appropriate melanoma patient (SORT Level A, 10/10 approved).*

This expert panel recommends that the 31-GEP test be used as a best practice for prognostic information, risk stratification, informing decisions for SLN biopsy and other management decisions for the appropriate melanoma patient. The panel amended the initial draft statement from using the term “standard of care” to “best practice” as more appropriate for integration into the clinical setting.

There was also some variance in the panel as to who was deemed an appropriate patient. The panel unanimously concluded that the 31-GEP test is most beneficial for patients with T1a high-risk tumors, T1b-T3 tumors, and patients with SLN biopsy negative results.<sup>50,51</sup> Literature has shown that 31-GEP testing reveals high-risk patients with low stage tumors,<sup>16,25,27,51</sup> which can be used to escalate care, including increased frequency of clinic visits, more extensive lab work, or repeated surveillance imaging. Similarly, the test can inform decisions for SLN biopsy and other invasive or extensive interventions for low-risk patients.<sup>28,34-36,51</sup> There is also a benefit for 31-GEP testing for patients who receive SLN biopsy and have a negative result. Gastman et al<sup>51</sup> found that the 31-GEP test significantly stratified SLN-negative patients into differential risk groups. This study identified 70% of SLN-negative patients who experienced metastasis, 71% of whom experienced recurrences, and 79% of whom experienced melanoma-specific mortality events as 31-GEP Class 2.<sup>51</sup> Another study reported that of SLN-negative patients, those who received routine imaging after high-risk 31-GEP results experienced earlier diagnosis of recurrence and lower tumor burden.<sup>50</sup>

Based on current evidence, the panel also concluded that the 31-GEP test is not indicated for patients with melanoma in situ, invasive melanoma measuring less than 0.3 mm, or a metastatic melanoma diagnosis.<sup>52</sup> There is also insufficient evidence at this time to discuss the impact of the 31-GEP test results on decisions regarding adjuvant therapy.

## Conclusion

The expert consensus panel conducted a comprehensive literature review and developed 9 consensus statement on the clinical efficacy, use, and accuracy of the 31-GEP test in providing prognostic information for invasive melanoma. The 31-GEP test has also demonstrated efficacy when the thickness or other traditional factors of melanoma are unknown. When integrated with traditional staging methods, the 31-GEP test can accurately inform decisions to recommend SLN biopsy and is more accurate than online nomograms. The panel concluded that the robust existing literature on the 31-GEP test strongly supports its use as a best practice for the appropriate melanoma patient.

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## Potential conflicts of interest

The authors declare the following conflicts of interest:

Clay Cockerell, MD, MBA, JD, is a consultant for SkinCure Oncology and serves on the advisory board for Dermtech.

David Cotter, MD, PhD, has served as an advisor, consultant, and/or speaker for AbbVie, Arcutis, Boehringer Ingelheim, Bristol Myers Squibb, Castle Biosciences, Dermavant, DermTech, Galderma, Janssen, Journey, LEO Pharma, Novartis, Pfizer, Regeneron, Sanofi, and UCB, and has served as a study investigator for AbbVie, Castle Biosciences, Celgene, Corevitas, Dermavant, Galderma, Lilly, Novartis, Prose, Regeneron, and Sanofi.

Aaron Farberg, MD, is an advisor and investigator for Castle Biosciences.

Laura Ferris, MD, PhD, is a consultant for DermTech.

Mark Kaufmann, MD, is a consultant for Apogee Therapeutics, Almirall, Avita Medical, Biofrontera, Botanix, Dermtech, Feldan Therapeutics, Incyte, Novan, Novartis, Nuvidia, Regeneron, Sanofi, Sun Pharmaceuticals, UCB, Veradermics, and Verrica.

Sancy Leachman, MD, PhD, has received an unrestricted educational grant from Castle Biosciences for support of the War on Melanoma public health campaign, and has served as a consultant for Orlucent, VeriSkin, Pathology Watch, and Merck.

Jason Rizzo, MD, PhD, has served as an investigator, consultant, and/or speaker for Arthrex, Castle Biosciences, Foundation for Research and Education in Dermatology, Kerecis, Smith+Nephew, and Triangulate Labs.

Todd Schlesinger, MD, is an investigator, consultant and speaker for Abbvie, Almirall, Apogee, Biofrontera,

Galderma, Bristol-Myers Squibb, Eli Lilly, SUN Pharma, Janssen, Boehringer Ingelheim, Pfizer, Sanofi-Regeneron, UCB, Castle Biosciences, Arcutis, ASLAN, Incyte, Sanofi, Janssen, Highlitll, Medicus, Novartis, Biofrontera, Takeda, Cara, and Castle Biosciences, and serves as a consultant/speaker for RBC Consultants, Dermsquared, Verrica, MJH Life Sciences, Beiersdorf, HTL Biotechnology, SkinCure Oncology, Chronicle Medical Software, and Flint Clinical.

Mark Lebwohl, MD, is an employee of Mount Sinai and receives research funds from Abbvie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Cara therapeutics, Dermavant Sciences, Eli Lilly, Incyte, Inozyme, Janssen Research & Development, LLC, Ortho Dermatologics, Pfizer, Sanofi-Regeneron, and UCB, Inc., and serves as a consultant for Almirall, AltruBio Inc., AnaptysBio, Apogee, Arcutis, Inc., AstraZeneca, Atomwise, Avotres Therapeutics, Brickell Biotech, Boehringer-Ingelheim, Bristol-Myers Squibb, Castle Biosciences, Celltrion, Corevitas, Dermavant Sciences, EPI, Evommune, Inc., Facilitation of International Dermatology Education, Forte biosciences, Foundation for Research and Education in Dermatology, Galderma, Genentech, Incyte, LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Sanofi-Regeneron, Seanergy, Strata, Takeda, Trevi, and Verrica.

Darrell Rigel, MD, MS, has served as an investigator, consultant, and/or speaker for Almirall, Beiersdorf, Inc., Castle Biosciences, Derm Tech International, Eli Lilly and Company, Ferndale Laboratories, Inc., Gore Range Capital, Johnson and Johnson Consumer Products Company, Kenvue, MoleSafe, Inc., Primus Pharmaceuticals, SciBASE, SkinCure Oncology, Sun Pharmaceutical Industries Ltd., and VYNE Therapeutics.

The remaining authors declare no conflicts of interest.

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