

Factors Affecting Dermatologists' Use of a 31-Gene Expression Profiling Test as an Adjunct for Predicting Metastatic Risk in Cutaneous Melanoma

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ABSTRACT

Importance: A 31-gene expression profile (31-GEP) test to predict metastatic risk in patients with cutaneous malignant melanoma has previously been validated and is available for clinical use. The impact of the availability of such a test on clinical decision-making has previously been studied. However, little is known about which factors play a role in clinicians' decision to utilize the test.

Objective: To determine factors affecting clinicians' decisions to utilize the 31-GEP test for metastatic risk stratification in patients with cutaneous malignant melanoma.

Design, Setting, and Participants: Dermatologists attending a national conference completed a series of questions based around four clinical vignettes using an audience response system. The vignettes and associated questions were designed to determine the impact of three factors—Breslow thickness, ulceration, and sentinel lymph node biopsy status—on the decision to order the 31-GEP test.

Main Outcomes and Measures: The percentage of respondents who would order the 31-GEP test in the various clinical scenarios was quantified. Differences between groups were assessed using the chi-squared test.

Results: A total of 181/187 individuals completed the survey (96.8% response rate). For tumors with a Breslow thickness ≥0.5 mm, a majority of respondents reported that they would recommend the 31-GEP test. Ulceration was associated with a statistically significant increase in the percentage of clinicians who would recommend the assay for all but the thickest (2.1 mm) tumors. A negative SLN was only associated with a statistically significant increase in the percentage of clinicians who would recommend the test for the thinnest (0.26 mm) tumors (22% to 34%, P=0.033).

Conclusions and Relevance: Ulceration appears to be the most important factor impacting clinicians when deciding to order the 31-GEP test to assess risk for melanoma metastasis.

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BACKGROUND

Cutaneous malignant melanoma (CMM) provides a significant challenge in terms of prognostication and post-diagnosis management. This is largely due to the inability of traditional staging systems to provide enough granularity to distinguish groups of patients with significantly different outcomes.[1,2] The clinical features that form the cornerstone of traditional American Joint Committee on Cancer (AJCC) staging systems are not as accurate in stratifying patients based on prognosis as they are in other malignancies. This is demonstrated by the fact that approximately two-thirds of melanoma-related deaths occur in sentinel-lymph node negative patients who are initially diagnosed with Stage I and II disease.[3] This apparent paradox may lead to a false sense of security on the part of the patient and the clinician, with lower-intensity follow-up plans for patients in remission—a detail underscored by the fact that the majority of recurrences are detected by patients themselves.[3,4]

These concerns highlight the need for new methods to more accurately group melanoma patients into prognostic categories. As such, there has been increasing interest in the use of molecular diagnostics and other "personalized medicine" techniques to better classify melanoma patients in terms of metastatic risk.[2,5,6]

One such technology is the 31-gene expression profile (31-GEP) test (DecisionDx-Melanoma, Castle Biosciences Inc., Friendswood, TX). This gene profiling system, which classifies patients as low-risk (Class 1) versus high-risk (Class 2) for metastasis based on differential gene expression, has previously been validated and has been shown to have additionally significantly improved predictive accuracy when combined with AJCC staging methods and guideline recommendations.[6] Despite the availability of this tool, relatively little is known about how dermatologists use the test clinically, particularly in terms of what factors clinicians consider when deciding whether to order the test. The purpose of this

TABLE 1.

Clinical Characteristics of Patient Vignettes			
Patient Vignette	**Age (years), Gender**	**Melanoma Location**	**Breslow Thickness (mm)**
1	45, Female	Right leg	0.76
2	42, Male	Right upper back	0.50
3	35, Male	Right arm	0.26
4	72, Female	Right neck	2.10

study was to determine which factors significantly impact clinicians' decisions to utilize the 31-GEP test to predict metastatic risk in patients with cutaneous malignant melanoma.

METHODS

Attendees at a national dermatology conference were sequentially presented with four patient vignettes, each a case of cutaneous malignant melanoma with a different Breslow thickness (Table 1). For each vignette, respondents were asked, via an anonymous audience response system, whether they would recommend the 31-GEP test for the patient. They were then asked to consider whether they would recommend the test for the same patient under two specific situations: 1) if the lesion were ulcerated and 2) if the patient had a negative sentinel lymph node biopsy. Respondents were also asked whether 31-GEP test results would affect their decision to recommend sentinel lymph node biopsy (SLNBx) in patients with 0.76-1.0 mm thick tumors

Additional questions were asked about years of clinical experience and previous familiarity with the 31-GEP test. Summary statistics were calculated for demographic variables. Chi-squared tests were used for comparison, with a *P*-value of $P<0.05$ considered significant. All analyses were performed using STATA statistical software (Version 15, College Station, TX). This study was Institutional Review Board exempt.

RESULTS

Sample Characteristics

A total of 181 of 187 individuals completed the survey (96.8% response rate). The sample consisted of mostly practicing dermatologists with relatively few trainees; roughly 50% of the sample had been in practice for more than 20 years. Two-thirds of respondents were previously familiar with the 31-GEP test.

Factors Impacting Clinicians' Decision to Order 31-GEP Test

For all vignettes with tumors with thickness of 0.5 mm or greater, the majority of respondents would recommend the 31-GEP test (Table 2). Only for the vignette with 0.26 mm tumor did a minority (22%) of subjects say they would recommend the

TABLE 2.

Percentage of Dermatologists Who Would Order 31-GEP Test in Different Clinical Scenarios			
Breslow Thickness (mm)	**Additional Vignette Characteristics**	**Percentage of Respondents Recommending 31-GEP Test**	***P*-value[b]**
0.26	Baseline[a]	22%	-
	Ulcerated	67%	<0.001
	SLN Negative	34%	0.033
0.5	Baseline[a]	78%	-
	Ulcerated	87%	0.019
	SLN Negative	66%	0.136
0.76	Baseline[a]	61%	-
	Ulcerated	80%	<0.001
	SLN Negative	65%	0.42
2.1	Baseline[a]	74%	-
	Ulcerated	72%	0.841
	SLN Negative	82%	0.141

[a]Baseline refers to vignette with no ulceration status or SLN status specified.
[b]Chi squared test comparing proportion who would order test if lesion were ulcerated or SLN status were negative compared to proportion who would order test at baseline for a given Breslow thickness.
mm = millimeters, 31-GEP = 31 Gene Expression Profiling test, SLN = sentinel lymph node biopsy.

test. For all but the thickest tumors (2.1 mm), the presence of ulceration was associated with a statistically significant increase in the proportion of respondents who would recommend the test (Table 2). For thin tumors (0.26 mm), the presence of ulceration increased the proportion of respondents who would recommend the test from a minority to a majority (22% to 67%, $P<0.001$). With the exception of 0.5 mm thick tumors, the presence of a SLN-negative biopsy was associated with an increased proportion of respondents who would recommend the test. However, the results were only statistically significant for 0.26 mm tumors, and even with an SLN-negative biopsy at this thickness, only a minority of clinicians would recommend the test (22% to 34%, $P=0.033$, Table 2).

Impact of 31-GEP Test Results on the Decision to Refer for SLNBx

When presented a scenario in which a hypothetical patient with a Stage T1b, 0.76-1.0 mm thick melanoma underwent 31-GEP testing which returned with a Class 1 (low-risk) result, 91% of respondents reported that this result would make them less likely to recommend a SLNBx. Conversely, when the scenario was altered to reflect the same patient but with a Class 2 (high-risk) 31-GEP result, 81% of respondents stated that this result would make them more likely to recommend a SLNBx (Figure 1).

DISCUSSION

Due to the fact that the majority of melanomas are diagnosed at an early stage, a sizeable fraction of melanoma-related deaths occur in patients initially diagnosed with early-stage disease.[3] Molecular diagnostics, such as the 31-GEP test, have shown potential in identifying these individuals with "low-stage" disease who have a more aggressive lesion and thus might benefit from increased intensity of management.

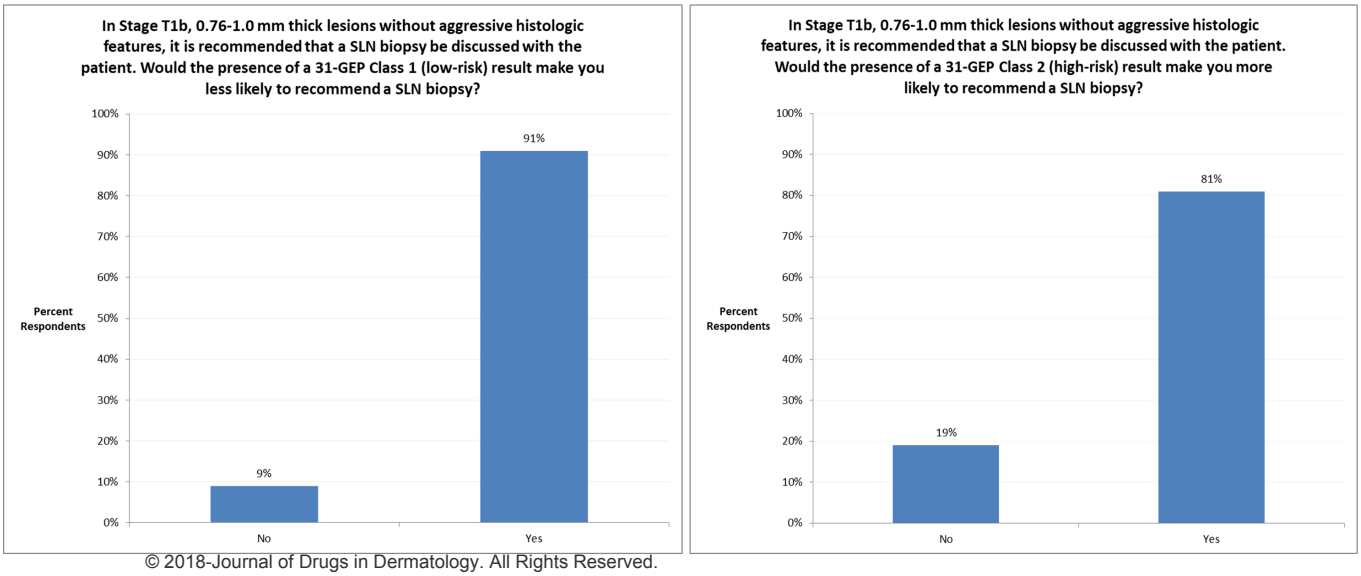
The 31-GEP test has previously been shown to add significant prognostic value when used in combination with traditional melanoma staging methods, such as sentinel lymph node status.[7] Prior work has shown that the 31-GEP test has the ability to change management in roughly half of tested patients, and that the results inform sound changes in the clinical management of melanoma.[2]

The results of this analysis add insight into the real-world context of how clinicians use the 31-GEP test. Tumor thickness appears to play a role in the decision to order the test, with a thickness of 0.5 mm being an important cutoff. Beyond 0.5 mm of thickness, there does not appear to be significant further association between increasing thickness and likelihood of ordering the test.

The presence of ulceration appears to be the most important factor considered when ordering the 31-GEP test, leading to a statistically significant increase in the proportion of clinicians who would order the test in all but the thickest tumors. For thin tumors in particular, ulceration appears to have a significant impact on clinical practice, with a majority of respondents hinging their decision to order the assay in 0.26 mm tumors on the presence of ulceration.

With prior studies detailing that positive SLNBx only identifies one-third of CMM patients who experience melanoma-related mortality, one might expect a great potential for the 31-GEP test to identify high-risk lesions and possibly change management in patients with SLN-negative disease.[3] Interestingly, however, SLN-negativity does not appear to be as strong of a stimulus to order the assay as ulceration. It is not surprising that SLN-negativity would have a greater impact on

FIGURE 1. Impact of 31-GEP results on respondents' decision to refer Stage T1b cutaneous melanoma patients for sentinel lymph node biopsy.



decision-making in smaller, lower stage tumors. Since larger, higher-stage tumors are typically treated more aggressively according to available guidelines, these smaller tumors are the lesions where differentiating between less-aggressive and more-aggressive tumor biology becomes essential. However, it is unclear why SLN-negativity did not have a greater magnitude of impact on the decision to perform the assay.

Despite the minimal impact of SLNBx results on the decision to order the 31-GEP test, in a patient with no *a priori* SLNBx results, a majority of respondents stated that 31-GEP test results would impact their decision of whether to recommend a SLNBx. This is consistent with a prior study by Farberg et al in which Dermatology residents were queried as to whether Class 1 or Class 2 results would alter their likelihood of recommending SLNBx.[5] Taken together, these two studies suggest that in low-stage CMM, the results of the 31-GEP test have a significant and appropriate impact on management while remaining within the context of established guidelines. More research is needed to determine the actual incidence of SLNBx positivity in the subpopulations of Stage T1b CMM with Class 1 and Class 2 31-GEP results.

Limitations of this study include the fact that the sample of dermatologists attending an academic conference may not be representative of the larger population of practicing United States dermatologists. Additionally, the survey format of the study, while providing insight into some of the factors considered by dermatologists when ordering the 31-GEP test, did not include all potential factors and did not allow discernment as to why SLN-negative status did not have a significant influence on the decision to order the test.

CONCLUSION

The presence of ulceration and Breslow thickness ≥0.5 mm appear to be the most influential factors found in this study influencing the decision to order the 31-GEP test in patients with CMM. Despite the fact that two-thirds of CMM patients who develop metastases initially have a negative SLNBx, SLN-negative status does not seem to be a significant stimulus to ordering the test. Future studies should aim to understand the reasons for this and should also focus on uncovering other potential influences on the decision to utilize the assay.

DISCLOSURES

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