

Impact of a 31-gene Expression Profiling Test for Cutaneous Melanoma on Dermatologists' Clinical Management Decisions

Aaron S. Farberg MD,[a] Alex M. Glazer MD,[b] Richard White MS,[c] and Darrell S. Rigel MD MS[d]

[a]Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY
[b]National Society for Cutaneous Medicine, New York, NY
[c]Iris Interactive System, Cody, WY
[d]Department of Dermatology, NYU School of Medicine, New York, NY

ABSTRACT

Importance: Current guidelines for cutaneous malignant melanoma (CMM) provide general recommendations regarding surveillance while indicating that management should be tailored to patients' individual probability of recurrence. A 31-gene expression profile (31-GEP) test to predict metastatic risk has been previously validated, and classifies patients as either Class 1 (low risk) or Class 2 (high risk).

Objective: To determine the impact of the 31-GEP test's result on clinical decision-making.

Design, Setting, and Participants: Dermatology residents who attended a national educational conference were presented with clinical validity evidence for the 31-GEP. Respondents were given six CMM patient vignettes with descriptions of clinical features and answered questions about their willingness to recommend sentinel lymph node biopsy (SLNBx) or imaging based on each scenario. Additionally, respondents were asked to provide the Breslow thickness (BT), ranging from 0.7-1.5mm in 0.1mm increments, at which they would recommend SLNBx, imaging, or oncology referral.

Main Outcomes and Measures: The number of respondents who would recommend each management modality based upon three outcomes (no result, Class 1, or Class 2) was quantified. Differences between response groups were assessed using Fisher's exact test.

Results: The majority of respondents (62%, 57%, and 55%, respectively) indicated a 1.0mm BT as the guiding modality, reflecting adherence to current guidelines. After inclusion of a Class 2 result, the BT used to guide SLNBx, oncology referral, and imaging was changed in 47%, 50% and 47% of the responses, respectively, with 95%, 84% and 97% of the cases, respectively, changed in a risk-appropriate direction (decreased BT). Based on a 31-GEP Class 1 or Class 2 result, risk appropriate recommendations were more likely to be made for each management modality tested in five of the six patient vignettes ($P<0.05$).

Conclusions and Relevance: The 31-GEP test had a significant and appropriate impact on management while remaining within the context of established guidelines.

J Drugs Dermatol. 2017;16(5):428-431.

BACKGROUND

Following a diagnosis of cutaneous malignant melanoma (CMM), patients are often guided for subsequent management by their dermatologist and national guideline recommendations.[1,2] Based upon staging classification for CMM, guidelines recommend diagnostic tests and additional evaluation which may provide defined treatment protocols, surveillance, and follow-up. Unfortunately, these recommendations are often similar across several tumor stages in part because of the inability to precisely stratify different risk groups that may have markedly different outcomes.

The push for personalized medicine has led to considerable advances in the guidelines and staging of CMM, including the recognition of the prognostic value of unique patient characteristics such as mitotic rate, ulceration presence, and sentinel lymph node biopsy (SLNBx) status.[3] Technology has already been demonstrated to augment dermatologists' clinical decision making for this tumor.[4] Molecular-based techniques have been shown to provide additional information for CMM as has been noted in many other tumors.

A 31-gene expression profile (GEP) test (DecisionDx-Melanoma, Castle Biosciences Inc., Friendswood, TX) was developed to predict whether a patient is at low-risk (Class 1) or high-risk (Class 2) for metastasis based on their primary CMM tumor biology.[5,6] The prognostic accuracy of the 31-GEP was previously reported in several prospectively planned multicenter studies and contributes significant additional information when considered in combination with current AJCC staging criteria and guideline recommendations.[5-8]

Although the 31-GEP has demonstrated reproducibility and clinical validity in assessing recurrence risk, another important aspect of molecular testing is clinical utility – the impact of the test results on clinical decision making. We sought to

TABLE 1.

Clinical Characteristics of Patient Vignettes

	Age, Sex	Stage	Tumor Location	Excision/Biopsy	Breslow Thickness	Ulceration	Mitotic Rate	History
1	42 years, female	IA	Right arm	Wide local excision	0.6 mm	Not ulcerated	No mitoses	No history
2	62 years, male	IB	Abdomen	Wide local excision	0.54 mm	Ulcerated	No mitoses	Personal history
3	69 years, male	IB	Mid-chest	Wide local excision	0.76 mm	Ulcerated	No mitoses	Personal history
4	45 years, male	IB/IIA	Left upper arm	Shave biopsy	Unknown (>0.5 mm)	Ulcerated	No mitoses	No history
5	61 years, female	IB	Left cheek	Wide local excision	0.9 mm	Ulcerated	>1/mm2	No history
6	38 years, female	IIA	Right chest	Wide local excision	1.2 mm	Ulcerated	No mitoses	No history

investigate the effect of prognostic molecular profiling of CMM in an attempt to further understand its effect on the clinical management decision-making process of dermatology resident physicians.

METHODS

Attendees at a national dermatology conference were asked to respond to a series of questions following an educational presentation on the 31-GEP test. Provided with patient information exclusive of tumor thickness, respondents were asked to identify the Breslow thickness (BT; ranging from 0.7-1.5 mm in 0.1 mm increments) at which decisions about SLNBx, imaging (including X-ray, ultrasound, computed tomography, and/or positron-emission tomography) and oncology referral would be made. Additionally, responses were obtained about willingness to utilize SLNBx or imaging based on six patient vignettes with variable clinical characteristics (Table 1). Of 172 attendees, 169 dermatology resident physicians completed the survey (99% response rate). Results were quantified and differences between response groups were assessed using a T-test or Fisher's exact test where appropriate. Institutional Review Board approval was waived for this study.

RESULTS

Impact of 31-GEP on Tumor Thickness-based Referral to SLNBx, Oncology, and Imaging

Respondents were provided the description of a 30-year-old male with a thigh lesion that was biopsy confirmed melanoma, without ulceration or atypical features, and no family or personal history of skin cancer. We evaluated the BT at which respondents would recommend SLNBx, imaging, and medical oncology referral given that results of the 31-GEP were either not provided, a Class 1 outcome, or a Class 2 outcome.

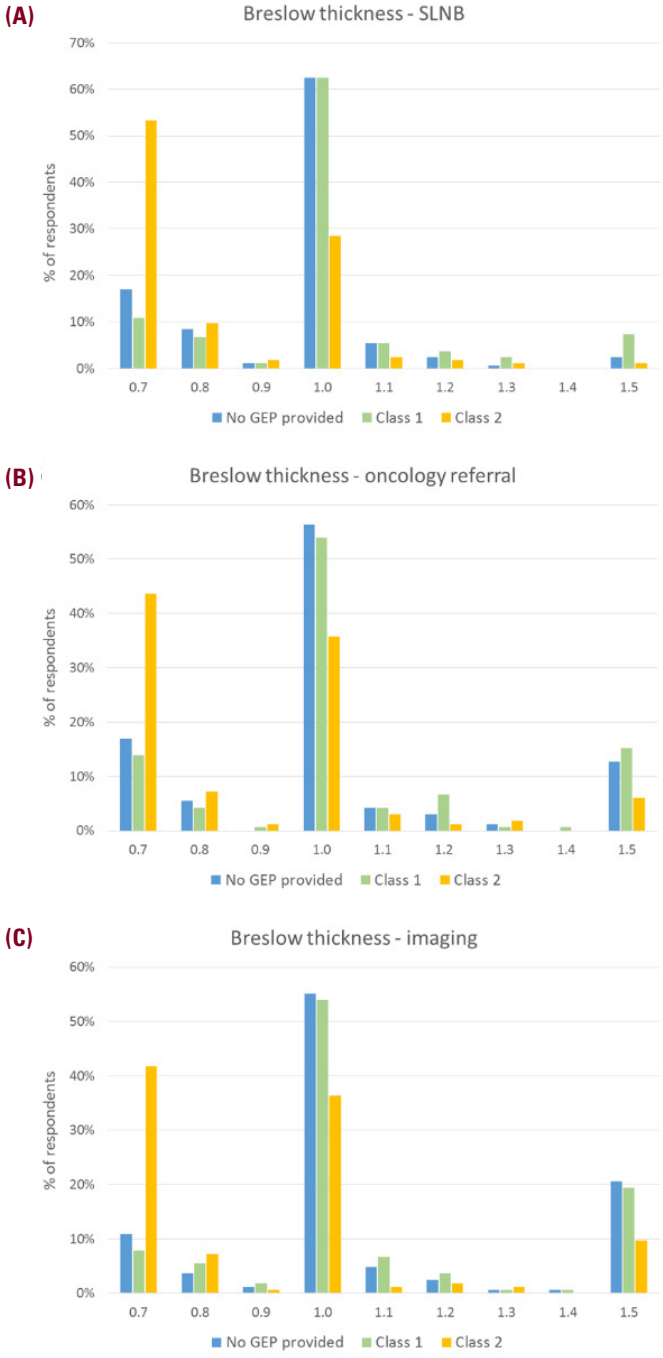
When 31-GEP results were not provided, 62%, 57%, and 55% of respondents used a BT of 1.0 mm as the inflection point to manage a patient with SLNBx, oncology referral or imaging, respectively (Figure 1). When respondents were provided with a Class 1 result in addition to clinical data, similar numbers of respondents (62%, 54% and 53%, respectively) again chose 1.0mm as the inflection point for implementing SLNBx, oncology referral and imaging. In contrast the most commonly selected BT with a Class 2 result was 0.7mm, where 52%, 42%, and 41% of respondents indicated that they would refer for SLNBx, oncology or imaging, respectively compared to 17%, 17%, and 11% with no GEP results ($P<0.05$).

Overall, responses reflecting the BT inflection points for guiding SLNBx, oncology referral and imaging were changed 23%, 18%, and 19%, respectively, after inclusion of a Class 1 result, with risk-appropriate changes (increased BT) of 87%, 83%, and 59%, respectively, for each modality. Following the addition of a Class 2 outcome to patient characteristics, the initial BT used to guide SLNBx, medical oncology referral, and imaging was changed in 47%, 50%, and 47% of the responses, respectively, with 95%, 84%, and 97% of the cases, respectively, changed in a risk-appropriate direction (decreased BT).

Recommendations for SLNbx and Imaging Using Six Patient Vignettes

We examined the number of respondents who would recommend SLNBx and imaging for each of six patient vignettes of varying tumor characteristics (Table 1), comparing the number of recommendations without 31-GEP information to those based on a Class 1 or Class 2 result (Figure 2). For each vignette, a Class 1 designation resulted in a significant decrease in recommendations for both SLNBx and imaging ($P<0.05$) with the exception of patient #1. When given a Class 2 result, a significantly larger number of respondents recommended imaging in all cases and SLNBx in five of the six cases ($P<0.005$), as this procedure would already be considered for patient #6 given a BT>1 mm in accordance with current guidelines.

FIGURE 1. Breslow thickness inflection point analysis for implementation of (A) sentinel lymph node biopsy, (B) oncology referral, or (C) imaging based on results from the 31-GEP test. Bars reflect the percentage of respondents who would refer patients for each modality of management based upon three outcomes (no result/none, Class 1, or Class 2) from the 31-GEP test.



DISCUSSION

Progress has been made in the understanding of the molecular mechanisms of CMM, resulting in pioneering treatments and clinical trials based on gene-targeted therapies.[9] This understanding has also led to the identification and clinical use of novel prognostic molecular markers to improve risk stratification and tailor more effective management strategies in CMM patients.[5] While SLNBx is the most accurate independent prognostic parameter for patients with CMM,[10, 11] positive SLN status only identifies one-third of CMM patients who expire from their tumor.[12] Given that SLN positivity is less than 5% in thin melanomas,[13] having additional molecular information to more precisely identify patients that do not appear to be at higher risk for metastasis but may, in fact, be so due to genetic factors, is clinically useful.[14]

The validity of the 31-GEP test has been demonstrated in multiple studies, most recently in a comparison with the AJCC online risk calculator which showed that the test provided information that significantly augmented the better identification of high-risk early stage patients.[3,5-8,14] In the current study, we evaluated the clinical impact of the test on CMM management decisions of dermatology resident physicians. When 31-GEP results were not provided, most respondents adhered to current NCCN management guidelines by using a BT of 1.0 mm as the inflection point to recommend SLNBx. Adding 31-GEP test information to the clinical characteristics of the patient vignettes and inflection-point scenarios led to significant, risk-appropriate changes in management decisions in SLNBx, imaging, and oncology referral. These results demonstrate that the 31-GEP test positively influenced clinical management and patient care, as clinicians incorporated the additional data to modify their clinical recommendations, and the findings are consistent with a recent study that demonstrated that 31-GEP results were clinically utilized in a risk-appropriate manner.[14]

Limitations of this study include that the patient vignettes may have also oversimplified typical patient presentations of disease. Additionally, this study included only dermatology resident physicians who may be more likely to adopt new clinical and technological data compared to dermatologists that were further in their careers.

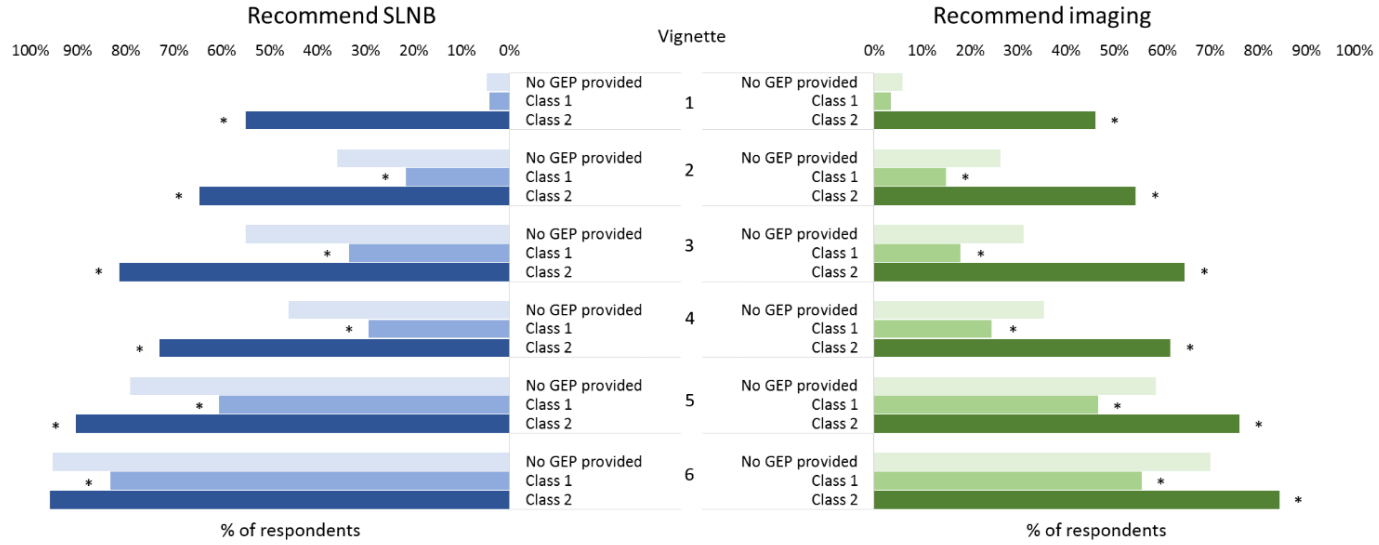
CONCLUSION

The NCCN and AJCC guidelines, coupled with the treating physician's judgment and patient preference, have been designed to guide the management of CMM. Our results suggest that the information provided by the 31-GEP test had a significant and appropriate impact on management while remaining within the context of established guidelines.

DISCLOSURES

Drs. Farberg and Rigel served as consultants to Castle Biosciences Inc. Dr. Glazer participated in a research fellowship which was partially funded by Castle Biosciences Inc. Mr. White has no conflicts of interest to disclose.

FIGURE 2. Recommendation of sentinel lymph node biopsy (left chart) or imaging (right chart) based on results from the 31-GEP test. Bars reflect the percentage of respondents who would recommend each modality of management for the patients with the clinical characteristics described in Table 1 based upon three outcomes (no result/none, Class 1, or Class 2) from the 31-GEP test. Asterisks reflect significantly different values ($P<0.05$, Fisher's exact test) compared to the "none" category.



REFERENCES

1. Coit DG, Thompson JA, Algazi A, et al. Melanoma, Version 2.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2016;14(4):450-73.
2. Bichakjian CK, Halpern AC, Johnson TM, et al. Guidelines of care for the management of primary cutaneous melanoma. American Academy of Dermatology. *J Am Acad Dermatol.* 2011;65(5):1032-47.
3. Balch CM, Gershenwald JE, Soong S, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol.* 2009;27(36):6199-6206.
4. Rigel DS, Mrinalini R, Yoo J, et al. Impact of guidance from a computer-aided multispectral digital skin lesion analysis device on suspicion to biopsy lesions clinically suggestive of melanoma. *Arch Dermatol.* 2012;148(4):541-543.
5. 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;21:175-83.
6. 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;72:780-5 e783.
7. Lawson DH, Russell MC, Wilkinson J, et al. Continued evaluation of a 31-gene expression profile test (GEP) for prediction of distant metastasis (DM) in cutaneous melanoma (CM). *J Clin Oncol.* 2015; 33 (suppl; abstr 9066).
8. Ferris LK, Farberg AS, Middlebrook B, et al. Identification of high risk cutaneous melanoma tumors is improved when combining the online AJCC melanoma patient outcome prediction tool with a 31-gene expression profile–based classification. *J Am Acad Dermatol.* In Press.
9. Ribero S, Longo C, Glass D, Nathan P, Bataille V. What is New in Melanoma Genetics and Treatment? *Dermatology.* 2016;232(3):259-64.
10. Balch CM, Gershenwald JE, Soong SJ, et al. Multivariate analysis of prognostic factors among 2,313 patients with stage III melanoma: comparison of nodal micrometastases versus macrometastases. *J Clin Oncol.* 2010;28:2452-2459.
11. Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med.* 2014;370:599-609.
12. Morton DL, Thompson JF, Alistair JC, et al. Final trial report of sentinel-node biopsy versus observation in melanoma. *N Engl J Med.* 2014;370:599-609.
13. Cordeiro E, Gervais MK, Shah PS, et al. Sentinel lymph node biopsy in thin cutaneous melanoma: A systematic review and meta-analysis. *Ann Surg Oncol.* 2016;23(13):4178-88.
14. 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):1599-1604.

AUTHOR CORRESPONDENCE

Alex M. Glazer MD

E-mail:..... alexglazer@gmail.com