ORIGINAL RESEARCH

Assessment of the 31-Gene Expression Profile Test by Dermatologists: A Cross-Sectional Survey from National Dermatology Conferences

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ABSTRACT

Background: The 31-gene expression profile (31-GEP) test uses 31 genetic markers obtained from the initial biopsy of a melanoma to assess melanoma-specific survival and sentinel lymph node positivity.

Objective: To assess the professional understanding, opinions, and clinical usage of the 31-GEP test by dermatologists.

Methods: Data from 589 unique dermatologists were collected during 2 virtual, nation-wide dermatology conferences via an 18-question survey on practice demographics and their clinical use and opinion of the 31-GEP test.

Results: Participants reported that integrating the 31-GEP test may benefit patients by increasing knowledge and understanding (72.5%), personalizing treatment options (58.8%), and easing uncertainty about the future (59.7%). Benefits of using the 31-GEP test included identifying true negative patients in high-risk populations (65.6%) as well as true positives in low-risk populations (70.6%).A majority of participants also noted that if a patient received a 31-GEP Class 2B result, they would escalate subsequent management even if the lesions were classified as T1 (61.4%) or AJCC8 Stage I (59.0%). 84.9% of participants were somewhat to very likely to use 31-GEP testing for patient management or recommend this test to a colleague.

Limitations: Potential respondent-selection and recall bias.

Conclusion: Dermatologists are increasingly integrating the 31-GEP test into their melanoma clinical management decisions. As the 31-GEP test becomes more prevalent in practice, patients may benefit from decreased anxiety and uncertainty from enhanced prognosis, decreased need for unwarranted procedures such as sentinel lymph node biopsy and optimized allocation of healthcare resources.

INTRODUCTION

The 31-gene expression profile test (31-GEP) (DecisionDx-Melanoma, Castle Biosciences, Inc., Friendswood, TX) analyses tissue collected from the initial diagnostic biopsy of a melanoma with an array of 31 genetic markers to assess prognosis. Prior studies have validated its ability to determine the risk of local/distant recurrence and sentinel lymph node positivity to assist in clinical decision-making.[1-3] The 31-GEP test is reimbursable under Medicare, certified by the Clinical Laboratory Improvement Amendments (CLIA), and was ordered over 16,000 times during 2019.[1,4] Given the increasingly wide-spread use of 31-GEP, the purpose of this study was to assess the professional understanding, opinions, and clinical usage of the 31-GEP test by dermatologists.

METHODS

The survey was available electronically via a website link during 2 national Dermatology conferences from October 29, 2020 to November 1, 2020 and January 16-24, 2021. Participants were asked to complete an 18 question survey regarding practice demographics, factors considered prior to ordering 31-GEP, their integration of 31-GEP results into clinical management, and their opinions on the usefulness of the test. IRB approval was obtained. Participants were compensated for their participation. Any duplicates were removed prior to data analysis.

RESULTS

After removing non-US respondents, 589 participants were eligible for the final analysis. Over 65% of the participants were private practice dermatologists with 48.2% having at least 11 years of independent clinical practice (Table 1). 52.5% of participants diagnosed at least 20 new

Table 1. Participant Demographics. A majority of participants were practicing Dermatologists in a private practice setting with at least 11 years of independent practice experience. A majority of participants noted diagnosing <50 new melanomas in 2019 and ordering <20 31-GEP tests over a 12 month period.

Demographics (n = 458)	% (n)
Primary Specialty	
Dermatologist	89.5 (527)
Mohs Surgeon	9.2 (54)
Dermatopathologist	1.4 (8)
Years of Training	
Resident	20.5 (121)
1-10 years	31.2 (184)
11-20 years	19.4 (114)
21-30 years	16.0 (94)
>30 years	12.9 (76)
Practice Type	
Private Practice	65.2 (384)
Academic	24.1 (142)
Multispecialty Group	7.1 (42)
Dermatology Group	1.4 (8)
Government	1.0 (6)
Other‡	1.0 (6)
How many newly diagnosed melanoma patients did you see in 2019?	
<20	47.5 (280)
20-50	41.1 (242)
51-100	8.7 (51)
101-200	1.9 (11)
>200	0.8 (5)
In the past 12 months, how many times have you ordered the Castle 31-GEP test?	
0	54.8 (323)
1-20	42.6 (251)
21-50	2.2 (13)
51-100	0.3 (2)

‡Other Practice Types: Unemployed (1), Volunteer (1), Locum Tenens (1), Retired (3)

melanomas in 2019 with 42.6% ordering between 1 and 20 31-GEP tests within the past 12 months.

A majority of participants reported that integrating the 31-GEP test may benefit patients by increasing knowledge and understanding (69.9%), personalizing treatment options (57.9%), and easing uncertainty about the future (58.6%) (Table 2). Even for patients with the lowest risk of recurrence (i.e. Class 1A), 65.9% of participants reported potential benefits for ameliorating patients' anxiety and 45.8% reported increasing confidence in their management. Of the participants that offer the 31-GEP test to patients, 33.3% reported patients expressed no concerns with the test. If concerns were noted, the most common was the potential cost (30.9%).

Study participants reported that benefits of using the 31-GEP test included identifying true negative patients in high-risk populations (65.9%) as well as true positives in low-risk populations (70.1%). Additional benefits included using test results to determine referrals/follow-up frequency (36.3%) and informing discussion regarding potential sentinel lymph node biopsy (SLNBx) (36.0%). A majority reported Breslow thickness ≥ 0.8mm (68.6%) and patient age/sex/history (55.7%) were factored into their decision to order the test. A majority of participants also noted that if a patient received a 31-GEP Class 2B result (which has previously been found to carry increased risk for recurrence within 5 years[1]), they would escalate subsequent management even if the lesions were classified as T1 (61.0%) or AJCC8 Stage I (58.7%).

Respondents believed potential false positive Class 2B results (i.e. patients at high risk of recurrence within 5 years that do not develop recurrence/metastasis) may be due to prompt/early intervention (71.3%), surgical excision prior to metastatic event (66.0%), or host immune response (71.5%) with a minority (31.2%) believing the result was an intrinsic error with the 31-GEP test. Going forward, 84.9% of participants were somewhat to very likely to use 31-GEP testing for patient management or recommend this test to a colleague and 66.0% would recommend a friend or family member receive the test as part of their care.

DISCUSSION

Our findings suggest that a majority of Dermatologists not only positively view 31-GEP testing, but are also incorporating it into management of their melanoma patients. Participants noted that having 31-GEP Class results had psychosocial benefits by aiding the physician-patient counseling, reducing anxiety and increasing confidence in the care plan. Given the test is reimbursable under Medicare, this may also ameliorate some patient concerns regarding the potential cost of the test.

From a clinical perspective, the way the studied Dermatologists report using 31-GEP testing largely follows published appropriate-use criteria for the 31-GEP test.[6] Prior studies have determined the usage of the 31-GEP test with the strongest support in the literature was in informing discussions regarding the need for SLNBx (A-Strength SORT recommendation[7]) with additional recommendation for facilitating management decisions of T1 and T2 melanomas and length of follow-up,[6] which is consistent with our results. Participants also reported confidence in the test with a minority

Table 2. Participant Reponses to Survey Questions.

Survey Question	% (95% CI)
What benefits do you think your patients gain from the Castle 31-GEP test results? (Select all that apply)	
Increased knowledge and understanding	69.9 (66.2-73.7)
Relief from uncertainty about future	58.6 (54.6 – 62.6)
More personalized treatment options	57.9 (53.9 – 61.9)
Information relevant to life planning	43.6 (39.6 – 47.6)
None	6.6 (4.6 – 8.6)
Most T1a patients (89.3%) will receive a low-risk GEP score. Do you think there's value in a T1a patient receiving a low-risk Class 1A result? (Select all that apply)	
Yes, it relieves uncertainty for patients.	65.9 (62.0 – 69.7)
Yes, it makes me more confident in my treatment plan.	45.8 (41.8 – 49.9)
Yes, other.	5.8 (3.9 – 7.7)
No, there is no value.	16.0 (13.0 – 18.9)
Do patients ever express any concerns about having the Castle 31-GEP test performed or receiving the results of the test? (Select all that apply)	
No	33.3 (29.5 – 37.1)
Yes-Concerns about the accuracy of the test	11.4 (8.8 – 13.9)
Yes-Concerns about the cost of test	30.9 (27.2 – 34.6)
Yes-Concerns about the risks of test	2.9 (1.5 – 4.2)
NA- I don't offer the test to my patients	34.5 (30.6 – 38.3)
For prognostic testing, which of the following provides a benefit for patient care? (Select all that apply)	
Identifying a true negative in a high-risk population	65.9 (62.0 – 69.7)
Identifying a true negative in a low-risk population	33.6 (29.8 – 37.4)
Identifying a true positive in a high-risk population	54.2 (50.1 – 58.2)
Identifying a true positive in a low-risk population	70.1 (66.4 – 73.8)
None of the above	2.2 (1.0 – 3.4)
How do you use Castle 31-GEP information? (select all that apply)	
As part of my decisions for follow-up schedules and referrals	36.3 (32.4 – 40.2)
As part of my decision to recommend or not recommend a patient having an SLNB	36.0 (32.1 – 39.9)
To inform surveillance imaging	22.1 (18.7 – 25.4)
To inform treatment decisions	24.8 (21.3 – 28.3)
I don't use the Castle 31-GEP	45.0 (41.0 – 49.0)
Which of the following factors would make you MORE likely to order the 31-GEP? (Select all that apply.)	
Breslow thickness ≥ 0.8mm	68.6 (64.8 – 72.3)
Presence of ulceration	44.7 (40.6 – 48.7)
Negative sentinel lymph node biopsy	28.0 (24.4 – 31.6)
Mitotic rate ≥2/mm2	45.8 (41.8 – 49.9)

None of the above	19.0 (15.8 – 22.2)
Which of the following factors do you also take into account when deciding to order the 31-GEP? (Select all that apply)	
Patient Age/Sex/Clinical History	55.7 (51.7 – 59.7)
Histological subtype	44.1 (40.1 – 48.2)
Location of tumor	34.3 (30.5 – 38.1)
Clark level	37.7 (33.8 – 41.6)
None of the above	26.5 (22.9 – 30.0)
T1 patients with a Class 1A (lowest risk) Castle 31-GEP result have a five-year recurrence free survival rate (RFS) of 96.8%, compared to T1 patients with a Class 2B (highest risk) result who have an RFS of 64.6%. Would receiving a Class 2B result for a T1 patient change your treatment plan?	
yes	61.0 (57.0 – 64.9)
No	5.8 (3.9 – 7.7)
I'm not sure	33.3 (29.5 – 37.1)
Stage I patients with a Class 1A (lowest risk) Castle 31-GEP result have a five-year recurrence free survival rate (RFS) of 97.6%, compared to Stage I patients with a Class 2B (highest risk) result who have an RFS of 76.1%. Would receiving a Class 2B result for a Stage I patient change your treatment plan?	
yes	58.7 (54.8 – 62.7)
No	6.1 (4.2 – 8.0)
I'm not sure	35.1 (31.3 – 39.0)
A recently published meta-analysis of the performance of the 31-GEP (Greenhaw et al., JAAD, 2020) demonstrates that patients with a Class 2B result are 3 times more likely to have a metastatic event compared to patients with a Class 1A result. However, not all Class 2B patients will have a recurrence or metastatic event (false positive result). In your opinion, which of the following factors could contribute to the receipt of a high-risk GEP result for a tumor that does not subsequently develop a recurrence or metastasis? (Select all that apply.)	
Surgical excision completed before metastasis of the cancer	66.6 (62.7 – 70.4)
Host immune system	71.5 (67.8 – 75.1)
Early intervention	71.3 (67.7 – 75.0)
Incorrect GEP result	31.2 (27.5 – 35.0)
Other (please specify)[†]	1.9[†] (0.8 – 3.0)
If a close friend or family member were diagnosed with cutaneous melanoma, would you recommend that they get additional prognostic testing (such as gene expression profiling or GEP) to aid in their decision making and care?	
Yes	66.0 (62.2 – 69.9)
No	5.6 (3.7 – 7.5)
I'm not sure	28.4 (24.7 – 32.0)

How likely are you to use the Castle 31-GEP test for the care of your patients or to recommend the use of the test to a colleague?	
Very unlikely	4.4 (2.8 – 6.1)
Not likely	13.8 (11.0 – 16.5)
Somewhat likely	47.7 (43.7 – 51.7)
Very likely	34.1 (30.3 – 38.0)

†Insufficient follow-up time (1), possible sampling error from tissue biopsy (1), "something else" currently not understood (1), imperfect predictive value of gene profile (1)

attributing potential false-positives to intrinsic test errors and nearly 90% positively viewing, using, or recommending the test.

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Limitations of this study include potential respondent-selection bias and the retrospective nature of the study. However, the method of questionnaire delivery (i.e. during a nation-wide virtual conference) potentially minimized regional bias and the studied sample population has a relatively uniform distribution of practice experience.

CONCLUSION

Dermatologists are increasingly integrating the 31-GEP test into their melanoma clinical management decisions. As the 31-GEP test becomes increasingly prevalent in practice, patients may benefit from decreased anxiety and uncertainty from enhanced prognosis, decreased need for potentially unnecessary procedures such as SLNBx and optimized allocation of healthcare resources. Future studies will be needed to determine the impact that the 31-GEP test will have on Dermatology practices and patient outcomes when fully integrated into current melanoma clinical management algorithms.

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Skin Cancer Prevention Working Group:
The Skin Cancer Prevention Working Group is a multi-center collaboration of experts dedicated to the prevention of skin cancer. The Working Group consists of clinical and research specialists that have spent years investigating and understanding the diagnosis and management of melanoma and non-melanoma skin cancer.

The mission of the Working Group is to cultivate and analyze evidence-based research to better understand skin cancer pathophysiology, treatment, and prevention in order to be leaders in skin health education.

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