

Management Decisions Made by Physician Assistants and Nurse Practitioners in Cutaneous Malignant Melanoma Patients: Impact of a 31-Gene Expression Profile Test

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ABSTRACT

Importance: The 31 gene-expression profiling test (31-GEP) has been shown to provide useful prognostic information in patients with cutaneous melanoma. The test dichotomizes patients into lower risk (Class 1) or higher risk (Class 2) for melanoma metastasis. Previous studies have demonstrated the clinical utility of the test in impacting dermatologists' management decisions. Physician assistants and nurse practitioners (PA/NPs) account for a significant portion of dermatologic providers. The impact of a 31-GEP assay on clinical management has not been evaluated in this group.

Objective: To determine the impact of 31-GEP test results on management decisions made by dermatology PA/NPs for cutaneous melanoma patients.

Design, Setting, and Participants: 164 PA/NPs attending a national dermatology conference completed an online survey designed to determine the impact of 31-GEP test results on management decisions in a variety of clinical situations. Participants answered a series of questions related to six melanoma patient vignettes, each featuring different patient and lesion characteristics.

Main Outcomes and Measures: Proportion of PA/NPs who would recommend sentinel lymph node biopsy (SLNBx) or further imaging for each patient vignette (without 31-GEP results, with a lower risk result, or with a higher risk result). The effect of the test results on the follow-up intervals recommended by PA/NPs was also examined.

Results: In the majority of cases, a lower risk 31-GEP test result led to a statistically significant decrease in the proportion of PA/NPs who would recommend SLNBx, imaging, or quarterly follow-up. Conversely, a higher risk 31-GEP result significantly altered management toward increased intensity (more recommendations for SLNBx, imaging, or quarterly follow-up) in all cases.

Conclusions and Relevance: The results of a 31-GEP test appear to significantly impact management decisions made by dermatology PA/NPs regarding SLNBx, acquisition of imaging, and follow-up for patients with cutaneous melanoma.

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BACKGROUND

Individuals with early-stage melanoma experience lower melanoma-specific mortality rates compared to those with more advanced (Stage III or IV) disease. However, despite this lower mortality rate, the highest absolute number of melanoma-related deaths occur in patients initially diagnosed with Stage I or II disease.[1] This is partially explained by the greater number of early-stage lesions that are diagnosed compared to more advanced cases. Recommendations for clinical management of early-stage melanoma are directed from population based risk of recurrence estimates.[2,3] Patients with Stage I-IIA disease receive fewer interventions (eg, sentinel lymph node biopsy (SLNBx), use of imaging, frequency of visits) than those with Stage IIB-IIC disease. Given the magnitude of patients diagnosed with early-stage disease who develop metastases, there is a need for additional stratification tools (beyond conventional methods such as AJCC staging) that can augment identification of Stage I and II patients who are at higher risk for subsequent metastasis.

A commercially available 31 gene-expression profiling (31-GEP) test (Decision Dx-Melanoma, Castle Biosciences Inc., Friendswood, TX) has been shown to be an accurate tool in identifying early-stage melanoma patients who are at higher risk for subsequent local recurrence, metastasis, or death.[4-9] This validated test dichotomizes patients into lower risk (Class 1) and higher risk (Class 2) groups based on differences in recurrence and surviv-

al rates that correspond to unique genetic expression patterns.[6] This classification system has been shown to work synergistically to improve prognostication when used in conjunction with previously established tools, such as the AJCC risk calculator.[10]

Although the ability of the test to risk-stratify patients is well established, its impact on clinician management is a newer area of study. Prior studies have demonstrated the clinical utility of a 31-GEP test on physician decision making.[11,12] The effect of the results on management decisions made by physician assistants and nurse practitioners (PA/NPs), who comprise a significant portion of the dermatologic workforce, has been less studied.[13] Thus, the goal of this study was to determine the impact of this technology on the management of cutaneous melanoma patients by this group.

METHODS

PA/NPs who attended a national dermatology conference completed an online survey with six melanoma patient vignettes. Each vignette presented patient age, gender, and history of skin cancer, along with lesion characteristics of Breslow thickness, ulceration, and presence of mitoses. Respondents answered a series of questions using pre and post-test methodology to evaluate the effect of lower and higher risk 31-GEP test results on management (decision to order SLNBx or radiologic imaging and recommended follow-up interval [q3 months, q6 months, q9 months, and q12 months]).

The primary outcomes were the proportion of respondents who would alter their decision to perform a SLNBx or obtain imaging with the addition of 31-GEP test results, as well as the proportion who would alter their recommended follow-up interval. McNemar's test was performed for assessing categorical variables, and the Wilcoxon signed rank test was performed for assessing ordinal variables. Clinical recommendations for lower and higher risk 31-GEP test results were compared to baseline (without 31-GEP test result).

RESULTS

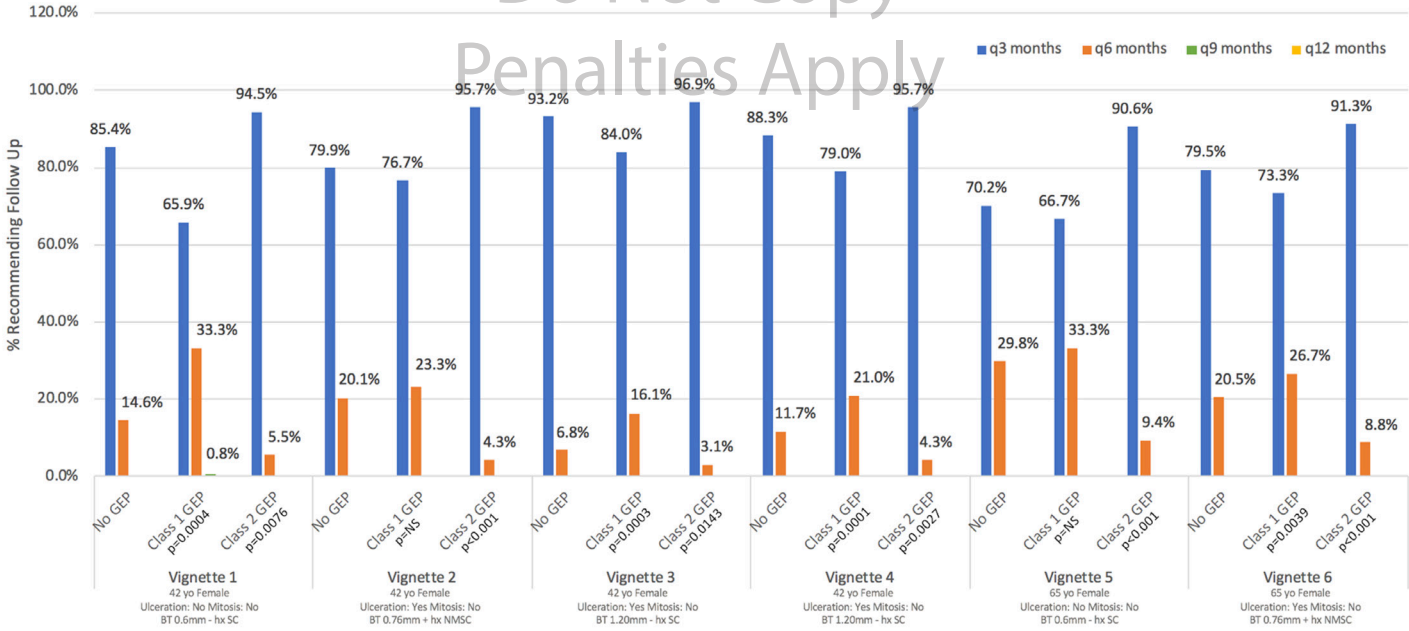
Respondent and Patient Vignette Characteristics

Overall, 164/195 (84.1% response rate) PA/NPs completed the survey. Of the respondents, 121 were PAs (73.8%) and 43 were NPs (26.2%). On average, participants reported being in dermatologic practice for 1.6 years (range, 0-4 years). Melanoma patient vignette characteristics and overall results are summarized (Table 1 and Figure 1).

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

A lower risk 31-GEP test result led to a statistically significant decrease in the proportion of SLNBx recommended by respon-

FIGURE 1. Effect of 31-GEP test results on PA/NP recommendation for melanoma patient follow-up interval.



*Analyses performed via Wilcoxon signed rank test. NS = Not significant. BT = Breslow thickness.

dents in 5 of 6 vignettes. For all vignettes with a higher risk 31-GEP test result, there was a statistically significant increase in SLNBx recommendations.

Impact of 31-GEP Test Results on Decision to Recommend X-Ray or Ultrasound

A lower risk 31-GEP test result led to a statistically significant decrease in recommended imaging with x-ray or ultrasound in 5 of 6 vignettes. For all vignettes, a higher risk 31-GEP test result led to a statistically significant increase in the proportion who would recommend x-ray or ultrasound imaging.

Impact of 31-GEP Test Results on the Decision to Recommend CT, MRI, or PET Scan

A lower risk 31-GEP test result led to a statistically significant decrease in recommended imaging with CT, MRI, or PET scans in 5 of 6 vignettes. For all vignettes with a higher risk 31-GEP test result, there was a statistically significant increase in CT, MRI, or PET scan recommendations.

Impact of 31-GEP Test Results on Recommended Follow-up Interval

A lower risk 31-GEP result led to a statistically significant increase in the number of respondents who would recommend a longer follow-up interval in 4 of 6 vignettes. Similarly, a higher risk result was associated with a statistically significant increase in the proportion who would recommend shorter follow-up interval for all vignettes.

DISCUSSION

In order to be clinically useful, a new technology or test must impact management.

Previous studies have demonstrated the impact and clinical utility of a 31-GEP assay on management decisions made by dermatologists and residents.[11,12] The present study produced similar results in another group, dermatology PA/NPs, who may have less experience in pigmented lesion assessment and thus may gain even greater benefit from this adjunctive technology.

TABLE 1.

Impact of 31-GEP Results on the Decisions of 164 PA/NPs to Order Adjunctive Tests for Six Hypothetical Patients with Cutaneous Malignant Melanoma

	Melanoma Patient Vignette											
	42 yo female Thickness: 0.6 mm Ulceration: No Mitosis: No No hx of skin ca		42 yo female Thickness: 0.76 mm Ulceration: Yes Mitosis: No + hx of NMSC		42 yo female Thickness: 1.20 mm Ulceration: Yes Mitosis: No No hx of skin ca		42 yo female Thickness: 0.90 mm Ulceration: Yes Mitosis: >1/mm2 No hx of skin ca		65 yo female Thickness: 0.6 mm Ulceration: No Mitosis: No No hx of skin ca		65 yo female Thickness: 0.76 mm Ulceration: Yes Mitosis: No + hx of NMSC	
Recommend SLNBx:	%	p-value[a]	%	p-value[a]	%	p-value[a]	%	p-value[a]	%	p-value[a]	%	p-value[a]
No GEP	16.20%	_	43.90%	_	92.00%	_	84.60%	_	1.90%	_	53.40%	_
Class 1 GEP	4.70%	0.0026	21.50%	<0.001	79.60%	<0.001	63.60%	<0.001	5.00%	0.0625	31.70%	<0.001
Class 2 GEP	86.80%	<0.001	90.80%	<0.001	97.50%	<0.0117	96.30%	<0.001	78.90%	<0.001	90.00%	<0.001
Recommend X-Ray/US:	%	p-value[a]	%	p-value[a]	n/N %	p-value[a]	%	p-value[a]	%	p-value[a]	%	p-value[a]
No GEP	10%	_	20.70%	_	61.50%	_	52.80%	_	2.50%	_	28.60%	_
Class 1 GEP	0.80%	0.0005	10.40%	0.0025	39.10%	<0.001	32.10%	<0.001	1.90%	>0.80	16.20%	<0.001
Class 2 GEP	52.30%	<0.001	69.90%	<0.001	79.60%	<0.001	81.40%	<0.001	63.40%	<0.001	75.60%	<0.001
Recommend MRI/CT/PET:	%	p-value[a]	%	p-value[a]	%	p-value[a]	%	p-value[a]	%	p-value[a]	%	p-value[a]
No GEP	5.40%	_	21.30%	_	72.10%	_	54.70%	_	0.60%	_	23.10%	_
Class 1 GEP	0.80%	0.0703	12.30%	0.0125	43.20%	<0.001	34.00%	<0.001	1.90%	0.5	16.20%	0.0127
Class 2 GEP	79.70%	<0.001	87.70%	<0.001	95.70%	<0.001	95.10%	<0.001	80.10%	<0.001	84.50%	<0.001

[a] McNemar's Test
% = Percent. YO = year old. Hx = history. CA = cancer. NMSC = Non-Melanoma Skin Cancer. GEP = Gene-Expression Profiling. SLNBx = Sentinel Lymph Node Biopsy. US = Ultrasound. MRI = Magnetic Resonance Imaging. CT = Computerized Tomography. PET = Positron Emission Tomography.

The results of this study indicate that the additional information provided by a 31-GEP test alters the management decisions made by dermatology PA/NPs in a variety of clinical situations. In most situations, a lower risk 31-GEP result was associated with a significant reduction in recommendations for SLNBx and further imaging, as well as a propensity to lengthen the recommended follow-up interval. This has the potential to reduce costs and patient burden. It also offers the potential to avoid complications related to SLNBx in a population with a very low rate of SLNBx positivity.[14,15] Compared to baseline, a higher risk result was associated with a significant increase in recommendation for SLNBx, further imaging, and a shorter follow-up interval in all cases. These patients are at the highest risk for development of subsequent metastases and might benefit from closer monitoring than would typically be recommended for patients with Stage I or II disease. The results from this study suggests that 31-GEP test results could lead to targeted redistribution of resources to those patients at highest risk for recurrence.

When the results of this study are considered in the context of prior studies demonstrating similar changes in management among dermatologists and dermatology residents,[11,12] it is clear that a 31-GEP test can be appropriately applied by all dermatology professionals. These findings indicate that changes in real-world management due to 31-GEP test results have the potential to benefit both lower risk patients who could undergo fewer unnecessary tests and higher risk patients who could receive closer follow-up. In the current age of accountable care, where providers are increasingly assessed on the value of care provided, these findings are particularly meaningful.

Limitations to this study include the possibility that the clinical vignettes used are not comprehensive representations of real-world patient cases. Additionally, the sample of PA/NPs attending the national conference may not accurately represent the larger population of dermatology PA/NPs practicing in the United States.

CONCLUSIONS

The results of this study demonstrate that the availability of 31-GEP test results significantly influenced the decisions of dermatology PA/NPs to recommend SLNBx, radiologic imaging, and follow-up interval. Furthermore, in the majority of cases, respondents utilized the information to alter management in the appropriate direction (eg, decreased SLNBx and imaging with a lower risk result and increased SLNBx and imaging with a higher risk result), while remaining in the context of existing guidelines. This indicates that the assay has clinical utility among PA/NPs and suggests that the improved prognostic information provided by the test would have an appropriate impact on patient management, potentially leading to more efficient resource allocation.

DISCLOSURE

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REFERENCES

1. 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(7):599-609.Acad Dermatol. 2017;76(5):818-825.e813.
2. National Comprehensive Cancer Network. NCCN Guidelines in Melanoma. Version 2.2018. Published January 19, 2018.
3. Bichakjian CK, Halpern AC, Johnson TM, Foote Hood A, Grichnik JM, Swetter SM, et al.Guidelines of care for the management of primary cutaneous melanoma. *J Am Acad Dermatol.* 2011 Nov;65(5):1032-47.
4. Hsueh EC, DeBloom JR, Lee J, et al. Interim analysis of survival in a prospective, multi-center registry cohort of cutaneous melanoma tested with a prognostic 31-gene expression profile test. *J Hematol Oncol.* 2017;10(1):152.
5. Hsueh EC, Schwartz TL, Lizalek JM, Hunborg PS, Hurley MY, Hinyard LJ. Prospective validation of gene expression profiling in primary cutaneous melanoma. In: American Society of Clinical Oncology; 2016.
6. Greenhaw B, Brodland D, Zitelli J. Estimation of prognosis in invasive melanoma using a gene expression profile test. *Amer Coll Mohs Surg.* 2016.
7. 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(5):780-785.e783.
8. 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(1):175-183.
9. Zager JS, Gastman BR, Leachman S, et al. Performance of a prognostic 31-gene expression profile in an independent cohort of 523 cutaneous melanoma patients. *BMC Cancer.* 2018;18(1):130.
10. Ferris LK, Farberg AS, Middlebrook B, et al. Identification of high-risk cutaneous melanoma tumors is improved when combining the online American Joint Committee on Cancer Individualized Melanoma Patient Outcome Prediction Tool with a 31-gene expression profile-based classification. *J Am Acad Dermatol.* 2017;76(5):818-825.e813.
11. Farberg AS, Glazer AM, White R, Rigel DS. Impact of a 31-gene expression profiling test for cutaneous melanoma on dermatologists' clinical management decisions. *J Drugs Dermatol.* 2017;16(5):428-431.
12. Svoboda RM, Glazer AM, Farberg AS, Rigel DS. Factors affecting dermatologists' use of a 31-gene expression profiling test as an adjunct for predicting metastatic risk in cutaneous melanoma. *J Drugs Dermatol.* 2018;17(5):544-547.
13. Adamson AS, Suarez EA, McDaniel P, Leiphart PA, Zeitany A, Kirby JS. Geographic Distribution of Nonphysician Clinicians Who Independently Billed Medicare for Common Dermatologic Services in 2014. *JAMA Derm.* 2018;154(1):30-36.
14. Cordeiro E, Gervais MK, Shah PS, Look hong NJ, Wright FC. Sentinel lymph node biopsy in thin cutaneous melanoma: A systematic review and meta-analysis. *Ann Surg Oncol.* 2016;23(13):4178-4188.
15. Cook RW, Johnson C, Monzon FA. Determination of sentinel lymph node biopsy eligibility using a 31-gene expression profile test in melanoma patients. Poster presented at: American College of Mohs Surgeons Annual Meeting; May 3, 2018; Chicago, IL.

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