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ORIGINAL ARTICLE

Clinical impact of a 31-gene expression profile test for cutaneous melanoma in 156 prospectively and consecutively tested patients

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ABSTRACT

Objective: DecisionDx-Melanoma* is a 31-gene expression profile test that predicts the risk of metastasis in patients with primary cutaneous melanoma (CM). This study was designed to ascertain clinical management changes determined by the test outcome, which classifies CM patients being at low (Class 1) or high (Class 2) risk for recurrence.

Research design and methods: Medical charts were reviewed from 156 CM patients from six institutions (three dermatology and three surgical oncology practices) who were consecutively tested between May 2013 and December 2015. Clinical management data that were compiled and compared before and after receipt of the 31-gene expression test result included frequency of physical exams, frequency and modality of imaging, and referrals to surgical and medical oncologists.

Results: Forty-two percent of patients were Stage I, 47% were Stage II and 8% were Stage III. Overall, 95 patients (61%) were Class 1 and 61 (39%) were Class 2. Documented changes in management were observed in 82 (53%) patients, with the majority of Class 2 patients (77%) undergoing management changes compared to 37% of Class 1 patients ($p < 0.0001$ by Fisher's exact test). The majority (77/82, 94%) of these changes were concordant with the risk indicated by the test result ($p < 0.0001$ by Fisher's exact test), with increased management intensity for Class 2 patients and reduced management intensity for Class 1 patients.

Conclusions: Molecular risk classification by gene expression profiling has clinical impact and influences physicians to direct clinical management of CM patients. The vast majority of the changes implemented after the receipt of test results were reflective of the low or high recurrence risk associated with the patient's molecular classification. Because follow-up data was not collected for this patient cohort, the study is limited for the assessment of the impact of gene expression profile based management changes on healthcare resource utilization and patient outcome.

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Introduction

Post-diagnostic clinical management of cutaneous melanoma patients is guided primarily by National Comprehensive Cancer Network (NCCN) recommendations[1]. Using American Joint Committee on Cancer (AJCC) staging[2] to categorize patients, the NCCN recommendations provide general guidelines for the patient's initial evaluation and subsequent follow-up, including referrals to surgical oncology for sentinel lymph node biopsy (SLNB) consultation, referrals to medical oncology, frequency of clinical visits for history and physical examination (H&P), frequency and intensity of imaging for metastatic surveillance, and blood work. Despite their utility, these recommendations are often similar for several AJCC stages, which may have markedly different outcomes. For example, the current guidelines indicate the same follow-up regimen for Stage IIB up to Stage IV patients with no evidence of disease, but the risk of metastases in these two groups is significantly different[1]. Furthermore, many of the guidelines are rather open-ended and allow wide ranges of follow-up frequency (i.e., imaging recommended as often as quarterly but as infrequently as once per year) and modality of imaging [i.e., chest X-ray, computed tomography (CT) or positron emission tomography-computed tomography (PET-CT)] Due to the lack of specificity of these recommendations, over-management of patients with less biologically aggressive lesions may result, while individuals whose melanomas are more prone to recurrence are insufficiently evaluated. The consequence of a non-individualized evaluation approach is the possible delay in recognition and treatment of recurrent disease.

However, in recognition of these generalities, the current guidelines do recommend that a patient's surveillance and management should be tailored to their individual probability of recurrence[1]. Using AJCC stage as a benchmark for probability of recurrence is problematic given that (i) the

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majority of patients who ultimately die from their disease are diagnosed with Stage I or II melanomas[2,3]; (ii) the population-based risks associated with the AJCC stages are often broad and thus make the assessment of individual risk of recurrence and metastasis challenging[4]; and (iii) some of the staging criteria (tumor thickness, ulceration status, mitotic rate) and other clinical and pathological characteristics (regression, tumor-infiltrating lymphocytes) are inherently subjective, and misclassifications, some of which result in differential guideline-recommended management, have been documented[5–7].

Therefore, in order to enable risk-appropriate patient management in melanoma, more accurate prognostication of the biology of the tumor is required. For this purpose, a 31-gene expression profile (GEP) test was developed and has been clinically validated in several prospectively planned, multi-center studies analyzing more than 500 melanoma specimens to demonstrate its accuracy to predict whether a patient is at low-risk (Class 1) or high-risk (Class 2) for metastasis based on their primary tumor biology[8–10]. In addition to this demonstrated reproducible clinical validity, another important aspect of molecular testing is that the clinical utility – impact of the test results on clinical-decision making – of the test should be evaluated and reported with complete transparency to physicians, caregivers, and patients[11,12]. As a precedent, several high-quality molecular diagnostics for other types of cancer, including those for breast and colon cancers and a 15-gene expression profile for uveal melanoma, have demonstrated clinical utility in patient management[13–18]. To this end, we performed an IRB-approved retrospective chart review of 156 prospectively tested melanoma patients managed at three dermatology and three surgical oncology practices in the United States. The study evaluated clinical management plans, including initial workup, follow-up, and referral patterns before and after gene expression profiling. As described herein, we found that in the majority of the patients the test informed changes in management, and most of these changes were consistent with the risk of recurrence indicated by their Class 1 or Class 2 result.

Methods

Study protocol and patient cohort

After protocol approval through either a centralized or institutional IRB, medical charts were reviewed for 159 patients at six institutions (three dermatology and three surgical oncology practices). All patients were consecutively tested between May 2013 and December 2015. Inclusion criteria for the study included complete AJCC staging information, documented clinical management plans, and a diagnosis of melanoma prior to gene expression profiling. Three patients were excluded from final data analysis. Two of these patients were excluded due to 31-gene expression testing performed more than three years after diagnosis, thus minimizing the time during which the test result, which predicts 5 year metastatic risk, could realistically impact management. The other patient was excluded due to the absence of documented clinical management plan of care prior to molecular testing.

Clinical management parameters

Frequency of clinical visits (H&P), frequency and modality of imaging [chest X-ray, CT, PET-CT, magnetic resonance imaging (MRI) or ultrasound (US)], SLNB procedure recommendation and result (if performed), referral to surgical oncology, referral to medical oncology, and use and frequency of routine blood work were collected and compared pre- and post-GEP testing. Physician implemented management changes were categorized as either (1) increased or (2) reduced, dependent upon more or less frequent office visits, imaging, or requests for laboratory testing, or upon added or removed imaging modalities or referral to oncology. Documented changes were categorized as "increased" or "reduced" based on comparison of management plans before and after the GEP test. Responses for the SLNB consideration and referrals were recorded as binary (Y/N), and imaging, blood work, and office visit results were recorded specifying the type (e.g. X-ray, PET-CT, MRI, etc.) and frequency (e.g. weeks, months) of the surveillance interventions. Due to the leeway in current guidelines for the frequency of follow-up and imaging, all differences specified between the pre- and post-GEP responses were considered as changes of management.

Statistical analysis of surveillance changes

Data on changes observed for the surveillance parameters listed above were compared using Fisher's exact 2×2 contingency table analysis or Fisher's exact 2×3 contingency table analysis with Freeman–Halton extension.

Results

Patient characteristics

A total of 156 patients met the inclusion criteria for the current analysis. Clinical characteristics of this cohort are presented in Table 1. Overall, 95 (61%) patients were classified as Class 1 and 61 (39%) patients were Class 2 (Figure 1). The majority of patients were male (62%), had a median Breslow thickness of 2.0 mm, and a median age of 63 years. The majority of tumors had superficial spreading and nodular growth patterns and were found on the extremities, reflecting patterns observed in the general population of CM patients.

Of the 156 cases, 100 (64%) received care in surgical oncology practices and 56 (36%) were seen in dermatology practices. Comparing patients managed by surgical groups to those managed by dermatologists indicated that those seen by surgical oncologists tended to have lesions with greater risk factors, such as ulceration (35% vs. 14%; $p = 0.008$ by Fisher's exact test) and higher rates of mitosis (74% vs. 41%; $p < 0.001$ by Fisher's exact test) (Table 2). A larger percentage of patients managed by surgical oncology were also categorized as Class 2 by the 31-gene expression profile test (51% vs. 18%; $p < 0.001$ by Fisher's exact test).

Comparison of management changes

Eighty-two of 156 (53%) patients in the study had a documented change in management following the 31-gene

Table 1. Patient clinical characteristics.

Clinical characteristics	All cases ($N = 156$)
Median age (range), years	63 (26–91)
Gender	
Male	97 (62%)
Female	60 (38%)
AJCC stage	
I	66 (42%)
II	74 (47%)
III	13 (8%)
Unknown	3 (2%)
Breslow thickness	
Median (range), mm	2.0 (0.2–19.0)
≤1 mm	38 (24%)
>1 mm	115 (74%)
Mitotic index	
<1 mm^2	29 (19%)
≥1 mm^2	120 (77%)
Ulceration	
Present	43 (28%)
Absent	102 (65%)
Growth pattern	
Superficial spreading	54 (35%)
Nodular	38 (24%)
Desmoplastic/lentigo maligna	7 (4%)
Site	
Head and neck	35 (22%)
Trunk	38 (24%)
Extremity	83 (53%)

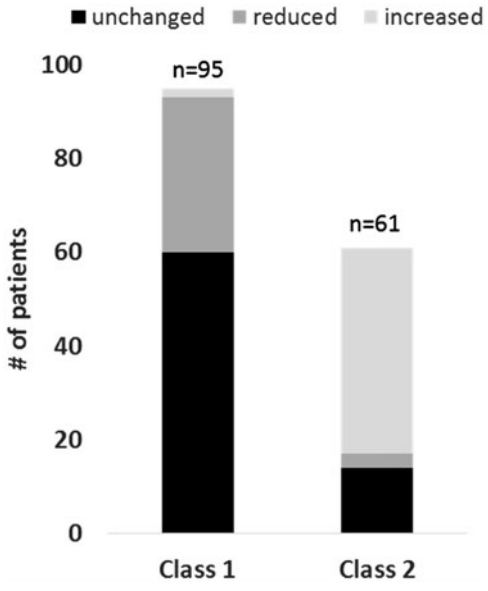

Figure 1. Distribution of patients in the study by gene expression profile test class, with changes in management intensity represented as unchanged, reduced or increased within the stacked bars for each class.

Table 2. Clinical characteristics according to surgical oncology vs. dermatology practices.

Clinical characteristics	Surgical oncology ($n = 100$)	Dermatology ($n = 56$)	p-value
Breslow thickness, median (range), mm	2.0 (0.5–19.0)	1.9 (0.2–6.5)	NS
Ulcerated, n (%)	35 (35)	8 (14)	0.008[a]
Mitotic rate >1/mm^2, n (%)	74 (74)	23 (41)	<0.001[a]
Class 2, n (%)	51 (51)	10 (18)	<0.001[a]

[a]Fisher's exact test.

expression profile result. As shown in Figure 1, the management of 35 of 95 (37%) Class 1 patients changed based upon the molecular test classification. Of those whose management changed, the majority of patients (33/35; 94%) changed to a reduced intensity management compared to pre-test management plans, while increased intensity was only documented for two (6%) patients. By comparison, 47 of 61 (77%) Class 2 patients had documented changes in surveillance or referral, with reduced intensity observed for only three (6%) cases and increased post-test management intensity for 44 (94%) cases. These results show that the management changes reflected lower or higher intensity regimens that occurred in the expected direction of change and were concordant with the 31-gene expression profile prediction of risk for most cases.

Stratifying results according to low-risk and high-risk AJCC stage, the 31-gene expression profile test confirmed a low-risk, Class 1 tumor biology for the majority (56%) of Stage I and IIA patients, resulting in no change in management. However, 13 of the 18 early stage patients who were identified as high-risk Class 2 had more intense management based on the result, primarily in the form of more frequent imaging requested by the surgical oncologist. By comparison, only 17% of the Stage IIB, IIC and III patients who had a Class 2 result had no change in their treatment regimen, and 11 of the 17 Class 1 patients within this increased stage cohort had reductions in their imaging protocols.

Comparison of changes by surveillance method

Patients with Class 1 and Class 2 outcomes were further compared within the management modalities of office visits, imaging, labs, or referrals. For each of these, significant and GEP risk-appropriate increases and decreases in management between Class 1 and 2 patients were observed ($p < 0.0001$, Fisher's exact test with Freeman–Halton extension; Table 3). Notably, the majority of management changes involved the office visits and imaging. The majority of patients (90 Class 1 and 41 Class 2) had no change in the frequency of office visits. While five (5%) Class 1 and two (3%) Class 2 patients had a reduction in the frequency of office visits, all 18 cases with increased office visits were Class 2. Overall, office visit frequencies for Class 1 and 2 patients were significantly different ($p < 0.0001$, Fisher's exact test with Freeman–Halton extension).

Significantly different changes in imaging with PET and/or CT were observed for the two classes ($p < 0.0001$, Fisher's exact test; Figure 2). Consistent with a more aggressive approach for molecularly determined high-risk patients, 38

Table 3. Comparison of changes by surveillance method.

	Class 1 ($n = 95$)		Class 2 ($n = 61$)	
Management modality	Reduce	Increase	Reduce	Increase
Office visits[a]	5	0	2	18
Imaging[a]	31	2	3	39
Labs[a]	0	0	0	9
Referrals[a]	4	0	0	8

[a]Significant difference between Class 1 and Class 2, $p < 0.0001$ using Fisher's exact test with Freeman–Halton extension.

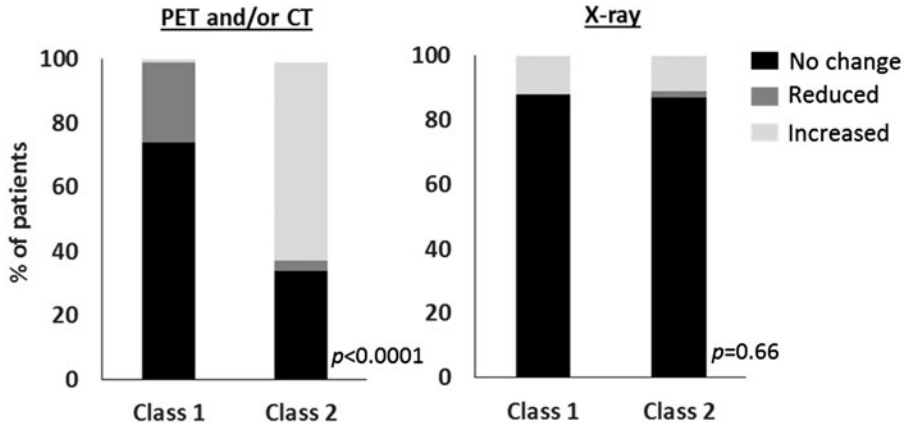

Figure 2. Distribution of patients in the study by changes in the frequency or number of imaging by PET and/or CT or X-ray.

out of the 40 patients who had increased PET-CT intensity were Class 2, while 24 of the 26 patients with decreased PET/CT regimen intensity were Class 1. Interestingly, there was not a significantly different change in the implementation of X-ray imaging between Class 1 and Class 2 cohorts ($p = 0.66$, Fisher's exact test). Among the 19 patients who had changes in chest X-ray protocols, all of the Class 1 cases and seven of eight Class 2 cases had increased frequencies of X-ray imaging. The substitution of more frequent X-rays in lieu of PET/CT may reflect a preference for less radiation-intensive imaging in the predicted low-risk Class 1 cohort.

Impact of GEP result on implementation of sentinel lymph node biopsy

SLN mapping and biopsy was performed for 112 of 156 (72%) cases analyzed. Ninety-nine (89%) patients had a negative SLN, while 13 (12%) had a positive result. In the SLN-negative group, 55 of the patients were Class 1, of whom none had an increase and 27 had a reduction in the intensity of management. Forty-four of the SLN-negative patients were Class 2, and 35 of these patients were given an increase in management intensity, while management was decreased for only two of these patients. By comparison, there were 13 SLN-positive cases with five patients having Class 1 results, none of whom received increased management, while two Class 1, SLN-positive patients experienced reductions in management intensity. Of eight Class 2/SLN-positive cases, the intensity of management was not decreased for any patients; however, management was intensified for four of these patients.

Of the 43 patients who did not have a SLNB performed, the procedure was discussed as part of their management for 28 patients. For the latter cases, three failed to map and four declined the procedure prior to testing with the 31-gene expression test. Only two patients within the study had SLNB utilization impacted by their 31-gene expression test results; each had a Stage IB tumor and a Class 1 prediction of risk. Notably, neither physician for these patients recommended SLNB prior to 31-GEP testing, but both recommended the procedure after having the assay performed. In both cases, the patient ultimately declined the procedure.

Discussion

The NCCN guidelines for management of melanoma patients provide workup recommendations generally based on stage of disease that include frequency of office visits, intensity of imaging for surveillance, and oncology referral. Patients with Stage I or IIA melanoma are generally managed with lower intensity surveillance strategies that include less frequent physician–patient interactions and little opportunity for intervention with adjuvant treatment, yet two out of three patients who die from melanoma are initially diagnosed with Stage I and II disease, and the majority of recurrences (up to 70%) are detected by the patient[19,20].

In the era of molecular diagnostics, the clinical utility of a diagnostic, prognostic or predictive molecular assay is determined by its ability to positively impact survival outcomes or inform physician changes in patient management. Along with the clinical validity and analytical validity of a test, clinical utility is an important determinant of the value of a diagnostic molecular assay. Within these parameters, it is critical to evaluate a test based upon its ability to i) accurately predict the outcome for which it was designed; ii) provide consistent accuracy across multiple studies, and iii) add value to the existing clinical tools[11,12,21]. The prognostic accuracy of the 31-gene expression profile test for CM, independent of standard clinical factors, was previously reported in two validation studies[8,9].

The results reported in this analysis of CM patients consecutively tested with the 31-gene expression profile indicate that this test informs appropriate clinical management and patient care. Within this multi-center study from both community practices and academic centers, a significantly different and increased intensity of surveillance was employed for high-risk, Class 2 patients compared to low-risk, Class 1 patients. Of the 156 cases included in the study, 82 had intensity of surveillance and/or referral patterns changed due to the results of the 31-gene expression profile test and, overall, 94% of the cases from either class that had a management change were in the expected direction of intensity based upon the test result.

Molecular classification also had an important impact on patient management following standard staging according to the AJCC guidelines, resulting in increased intensity of

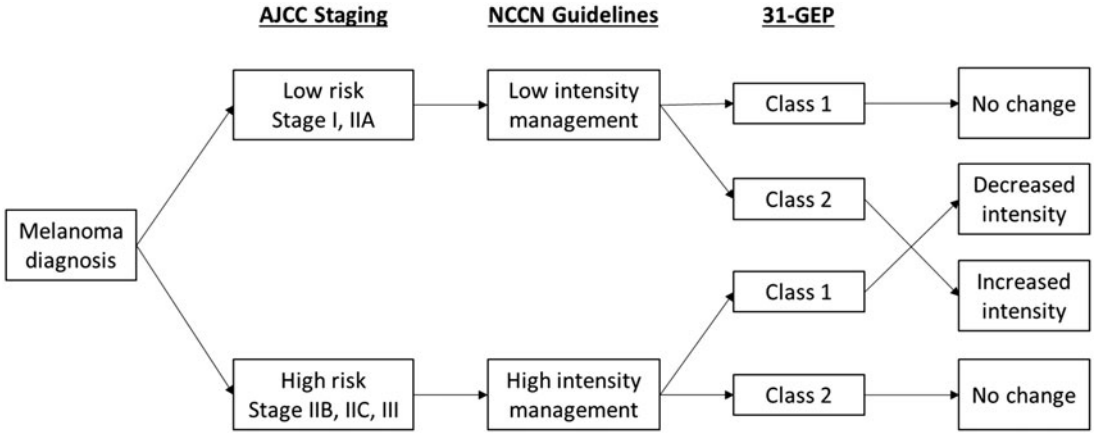

Figure 3. Changes in the intensity of management of low risk Stage I and IIA patients or high risk Stage IIB, IIC and III patients based upon the 31-gene expression profile (31-GEP) prediction of risk in the context of AJCC and NCCN guidelines.

surveillance and referral to oncology for early Stage I and IIA patients who had a Class 2 result, and reduced intensity of surveillance for later Stage IIB, IIC and III patients who had a Class 1 result according to the 31-gene expression test. The results indicate appropriate clinical use of the test in combination with current AJCC staging to identify (i) high-risk, early stage melanoma patients who would benefit from intensified management to identify metastatic disease as early as possible; and (ii) later stage melanoma patients who are less likely to develop systemic metastasis and would benefit from management of localized disease (Figure 3). Importantly, a growing body of data supports better efficacy of contemporary melanoma therapies when used to treat metastatic disease at a time of lower, compared to higher, tumor burden, which justifies the use of increased intensity of surveillance in those patients considered at high risk for metastases[22–24].

An important finding of the study was the minimal effect of the 31-gene expression profile results upon the use of the SLN biopsy procedure, and that test results were impactful following SLNB. The utility of the molecular test in combination with SLN status was previously reported, and showed that the 31-gene expression profile adds significant value by identifying 70–80% of SLN-negative patients who are Class 2 and thus have a high risk of metastasis[8]. Importantly, only two of the 156 cases analyzed had a change in SLNB utilization in which physicians offered SLNB to their patients after the test results; both of these cases were Class 1 which suggests that other factors prompted this management suggestion. Significantly, the study did not reveal any evidence that the 31-gene expression profile test results influenced physicians to change SLNB recommendations in their patients. The 31-gene expression profile did, though, impact the management of SLN-negative patients. Thirty-five of 44 (80%) Class 2/SLN-negative patients in the study were moved to an increased intensity surveillance regimen as a result of the high-risk molecular classification. Conversely, 27 of 55 (49%) Class 1/SLN-negative patients were assigned to reduced intensity surveillance programs.

One limitation of the study is the absence of follow-up data required to correlate the 31-gene expression profile classification with outcomes. However, the endpoint of this particular study was to analyze changes in clinical management resulting from the Class 1 or 2 assignments rather than patient outcomes. Although the prognostic accuracy of the test has been published previously in peer-reviewed manuscripts[8,9], future studies would benefit from the collection of follow-up data to show the impact of clinical practice adjustments on patient outcomes.

Conclusion

The prognostic accuracy of a 31-gene expression profile test for predicting the metastasis risk associated with CM tumors has previously been reported. The results of the study show that the genomic classification of melanoma with the 31-gene expression profile test changed clinical management in more than half of the tested patients, and that the changes implemented were consistent with the expected use of test results. Thus, surgical oncologists and dermatologists managing the melanoma patients included in the study used the results of the test to individualize management based on biological risk, increasing the intensity of surveillance in high-risk Class 2 patients and reducing the intensity of surveillance in low-risk Class 1 patients while still remaining within the context of established practice guidelines for melanoma patient management.

Transparency

Declaration of funding

This study was sponsored by Castle Biosciences Inc. The participating institutions received financial compensation to account for costs associated with the conduct of the study.

Declaration of financial/other relationships

C.E.J., D.J.M., B.M., K.M.O., R.W.C., and F.A.M. have disclosed that they are employees of Castle Biosciences Inc. and hold stock in the company. A.C.B., R.S.D., J.K.P, I.C., R.H., A.B., and A.M. received sponsorship and research funding from Castle Biosciences, Inc. A.C.B., I.C., and A.R.M. have served on the Speaker's Bureau for Castle Biosciences, Inc.

CMRO peer reviewers on this manuscript have received an honorarium from *CMRO* for their review work. Peer reviewer 1 has disclosed that he is a consultant to Dermtech Inc., Myriad Genetics, and Castle Biosciences. Peer reviewer 2 has no relevant financial or other relationships to disclose.

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