The prognostic 31-gene expression profile (31-GEP) test improves risk prediction in cutaneous melanoma (CM) patients within current AJCC stages

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Background

- Risk of progression and death in patients with CM is diverse and impacted by clinicopathologic features, including ulceration, Breslow thickness, and sentinel lymph node (SLN) involvement.[1]
- Prediction of risk needs improvement, as a substantial number of patients with low-risk clinicopathologic features have poor outcomes.[1]
- The 31-GEP test stratifies patients into low-risk (Class 1, 1A lowest risk) and high-risk (Class 2, 2B highest risk) groups for recurrence, distant metastasis, and melanoma-specific mortality within 5 years.[2-9]
- The 31-GEP has been used clinically to inform intensity of follow-up, including use of imaging for surveillance and consideration of adjuvant therapy. [10-15]
- The utility of the 31-GEP test to guide SLN biopsy decisions has been recently reported as Class 1A patients with T1-T2 melanoma have a low risk of SLN positivity.[16]

Objectives

- To determine if the 31-GEP test provides additional prognostic utility to AJCC 8th edition staging

Methods

- A pooled cohort of 901 archival CM samples (690 previously reported)[5] from 22 centers with clinicopathological and outcomes data were collected under an IRB-approved protocol and patient staging was updated to AJCC version 8.
- Primary outcomes measured were RFS (recurrence-free survival, the time from diagnosis to any regional or distant recurrence), DMFS (distant metastasis-free survival, the time from diagnosis to any recurrence beyond the regional nodal basin), and MSS (melanoma-specific survival, the time from diagnosis to a melanoma-related death).
- Patient characteristics were compared by Kruskal-Wallis F test or Pearson chi-square tests as appropriate.
- Survival was estimated by Kaplan-Meier analysis with log-rank test.
- Mulitvariate Cox regression analysis was used to evaluate prognostic impact of GEP and clinical/pathological features used for staging, including Breslow thickness, ulceration and SLN status. For proportional hazards analysis, Breslow thickness was measured as a continuous variable, while ulceration and SLN status were dichotomized.
- We compared 5-year MSS of Class 1A and Class 2B patients within each stage to reported AJCC 5-year MSS.

Results

Figure 1. 5-year MSS of 901 patients compared to AJCC 8th edition cohort

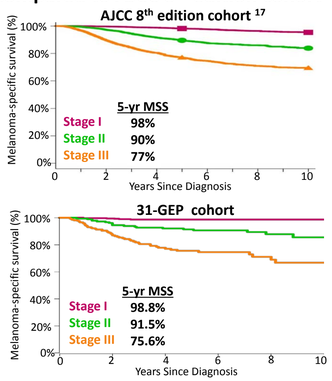
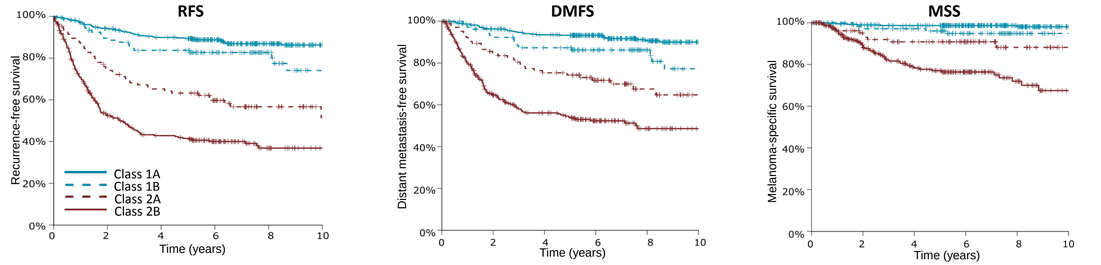


Table 1. Demographics of patients from 901 archival cutaneous melanoma cohort

	Combined (n=901)	Class 1A (n=391)	Class 2B (n=297)	p value
Median age, yrs (range)	60 (18-94)	56 (18-91)	64 (18-94)	p<0.0001
Median Breslow thickness, mm (range)	1.4 (0.9-29)	0.7 (0.1-12)	3.0 (0.3-29)	p<0.0001
Ulceration				
Present	262/901 (29%)	32/391 (8%)	177/297 (60%)	p<0.0001
Absent	529/901 (59%)	295/391 (75%)	100/297 (34%)	
Unknown	110/901 (12%)	64/391 (17%)	20/297 (7%)	
SLN status				
Positive	276/901 (31%)	63/391 (16%)	144/297 (48%)	p<0.0001
Negative	354/901 (39%)	136/391 (35%)	120/297 (40%)	
Unknown	271/901 (30%)	192/391 (49%)	33/297 (11%)	
AJCC Stage				
Stage I	400/901 (44%)	283/391 (72%)	30/297 (10%)	p<0.0001
Stage II	213/901 (24%)	44/391 (11%)	114/297 (38%)	
Stage III	288/901 (32%)	66/391 (17%)	153/297 (52%)	

Percentages reflect proportion of column. SLN, sentinel lymph node; AJCC, American Joint Committee on Cancer

Figure 2. Kaplan-Meier survival outcomes of 901 CM patients by 31-GEP Class



31-GEP Class	5-year RFS (95% CI)	Events (%)
Class 1A (n=391)	89% (86-93%)	48 (12%)
Class 1B (n=106)	84% (77-91%)	21 (20%)
Class 2A (n=107)	63% (55-73%)	44 (41%)
Class 2B (n=297)	42% (36-48%)	164 (55%)

31-GEP Class	5-year DMFS (95% CI)	Events (%)
Class 1A (n=391)	93% (91-96%)	32 (8%)
Class 1B (n=106)	87% (81-94%)	17 (16%)
Class 2A (n=107)	74% (66-83%)	31 (29%)
Class 2B (n=297)	54% (48-61%)	125 (42%)

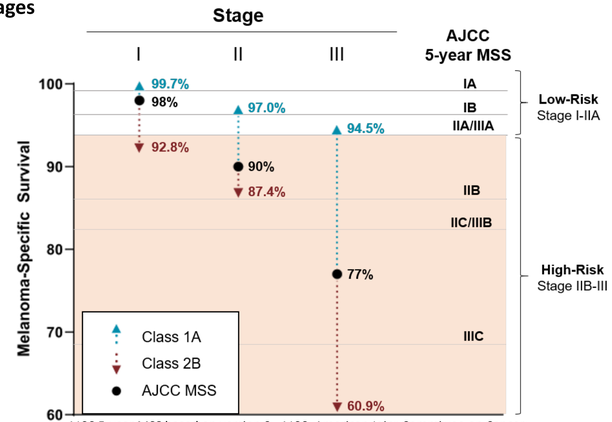
31-GEP Class	5-year MSS (95% CI)	Events (%)
Class 1A (n=391)	99% (98-100%)	6 (2%)
Class 1B (n=106)	96% (91-99%)	5 (5%)
Class 2A (n=107)	91% (85-97%)	10 (9%)
Class 2B (n=297)	77% (72-83%)	58 (20%)

Table 2. Multivariate Cox regression analysis of 31-GEP and clinicopathologic features

	RFS		DMFS		MSS	
Variable	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Breslow thickness	1.09 (1.01-1.11)	<0.0001	1.08 (1.04-1.12)	<0.0001	1.13 (1.08-1.18)	<0.0001
Ulceration	1.49 (1.14-1.94)	0.003	1.92 (1.41-2.61)	<0.0001	1.26 (0.78-1.18)	0.34
SLN positive	2.75 (2.15-3.53)	<0.0001	3.13 (2.34-4.19)	<0.0001	4.02 (2.46-6.55)	<0.0001
GEP Class 1B	1.27 (0.76-2.13)	0.36	1.43 (0.78-2.59)	0.24	2.14 (0.65-7.07)	0.21
GEP Class 2A	2.81 (1.85-4.28)	<0.0001	2.55 (1.53-4.23)	<0.001	4.14 (1.48-11.60)	0.006
GEP Class 2B	3.77 (2.60-5.48)	<0.0001	3.49 (2.23-5.45)	<0.0001	7.32 (2.94-18.24)	<0.0001

Hazard ratios for RFS, DMFS, and MSS calculated by Cox regression analysis. CI, confidence interval; SLN, sentinel lymph node; GEP, gene expression profile.

Figure 3. 31-GEP stratifies patients into low- and high-risk subset within AJCC stages



AJCC 5-year MSS based on version 8. AJCC, American Joint Committee on Cancer;
Low-risk and high-risk classification based on NCCN guidelines for patient management

Conclusions

- The 31-GEP is a significant and independent predictor of RFS, DMFS, and MSS in a cumulative cohort of 901 cutaneous melanoma patients
- Within AJCC Stages, 31-GEP further stratifies risk of melanoma-specific mortality
- The 31-GEP adds prognostic information beyond AJCC staging and provides a more comprehensive assessment of patient risk

References and Acknowledgements

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Disclosures

KRC, HGC, and RWC are employees and stockholders of Castle Biosciences, Inc.