Improved prognostic guidance by the 31-gene expression profile test for clinical decisions after a negative sentinel lymph node biopsy for patients with cutaneous melanoma

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Background

- Despite a good overall prognosis for patients with a negative SLNB, 10-24% will experience recurrence or metastasis, and melanoma-specific survival (MSS) rates range from 82-99%.[1-4] A subset of these patients (stage IIB-IIC) are currently eligible for adjuvant therapy, though it is unclear which patients will benefit and which patients do not need therapy.[5]
- The recent KEYNOTE-716 trial showed a benefit of adjuvant pembrolizumab in patients with stage IIB-IIC melanoma (9% RFS improvement), but 80% had an adverse event (16% grade 3 and higher), and 18% discontinued treatment due to adverse events.[5]
- **These data underpin a need for prognostic tools beyond clinicopathologic features to identify patients with high-risk tumor staging but low-risk tumor biology, or low-risk tumor staging but high-risk tumor biology, so that patients receive risk-aligned treatment.[1-2]**
- Multiple prospective and independent studies have shown that the 31-GEP test is a consistent and independent predictor of survival outcomes in large populations of patients with stage I-III CM, and that clinicians use the 31-GEP to guide patient management decisions.[3, 6-10]

Objective

In collaboration with the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program (covering 34% of the U.S. population during the study period) this study sought to:

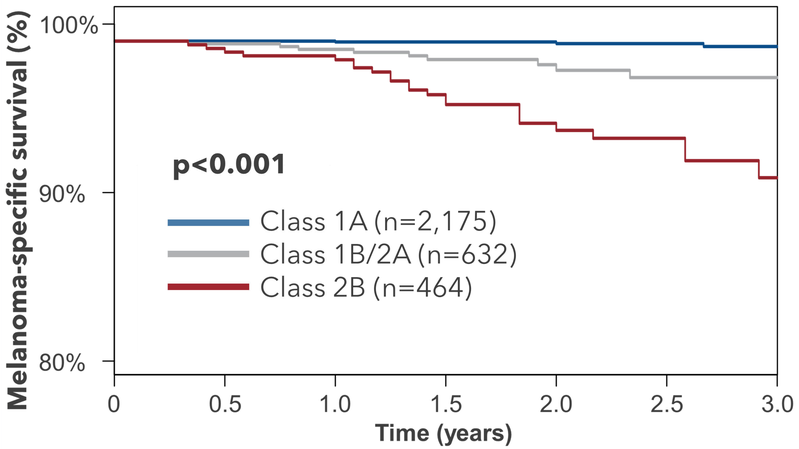
- **Demonstrate the performance of the 31-GEP to identify patients with high-risk tumor biology in an unselected, clinically tested cohort of patients with a negative SLNB.**

Methods

- SEER cancer registries linked CM cases diagnosed from 2016-2018 to data for patients with CM who were tested with the 31-GEP (n=3,271). Linkage was mediated by Information Management Services (an Honest Broker for the SEER registries). A de-identified dataset was used for this analysis. A focused analysis of SLNB negative patients was performed.
- Kaplan-Meier analysis with the log-rank test was used to analyze 3-year melanoma-specific survival (MSS). Multivariable Cox regression was used to identify factors associated with MSS.

Results

Figure 1. Using the 31-GEP in patients with a negative SLNB identifies those at highest risk of dying from their disease.

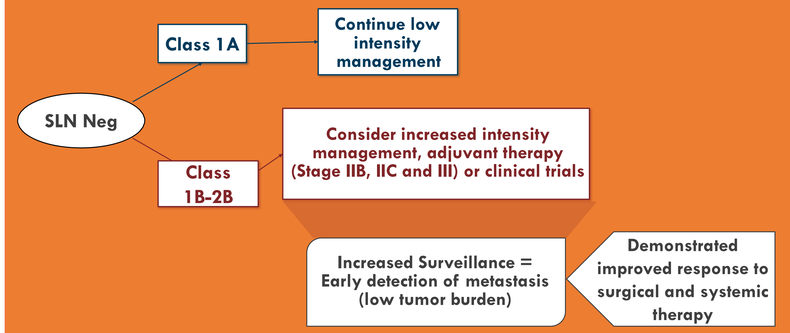


- Patients with Class 1A results had higher 3-year MSS (Class 1A: 99.7%; Class 1B/2A: 97.8%; Class 2B: 91.8%, p<0.001).
- **In the subset of patients with IIB-IIC disease (n=311), no Class 1A (0%, 0/38) patients died from melanoma compared with 6.7% (14/210; 8 IIB, 6 IIC) of Class 2B patients.**

Table 1. Multivariable analysis demonstrates independent and significant prognostic information compared to traditional staging factors

Melanoma-specific survival	Multivariable HR (95% CI)
31-GEP Class 1A	Reference
31-GEP Class 1B/2A	5.76 (1.42-23.41)
31-GEP Class 2B	10.50 (2.55-43.28)
Age (continuous)	1.05 (1.02-1.08)
AJCC Stage IA	Reference
AJCC Stage IB	1.48 (0.37-6.01)
AJCC Stage IIA	3.93 (1.10-14.12)
AJCC IIB	3.24 (0.82-12.86)
AJCC IIC	4.58 (1.09-19.22)

Clinical Impact



- Using the 31-GEP results to guide increased clinical management and surveillance for patients at high risk of melanoma-specific death may improve patient outcomes.

Conclusions

- In patients with a negative SLNB, the 31-GEP identifies patients more or less likely to die from their melanoma in the absence of adjuvant therapy, and the 31-GEP is a significant predictor of melanoma-specific death, even when accounting for substage.
- The 31-GEP can direct care to patients with high-risk tumor biology who are most likely to benefit from higher intensity management and away from those unlikely to benefit from adjuvant therapies to spare patients from adjuvant therapy-associated adverse events.

References

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- SK, CB, BM, MG, RC, and KC are employees and shareholders of Castle Biosciences, Inc.
- VP has no disclosures

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