Combining the 31-gene expression profile test for cutaneous melanoma with the American Joint Committee on Cancer staging identifies the highest-risk patients with stage I-II disease

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Background

- Cutaneous melanoma (CM) management guidelines are based on patients' recurrence risk by stage. Most newly diagnosed patients (88%) are node-negative (stage I-II) and considered low risk. However, due to the size of the group, the majority of melanoma-associated deaths each year occur in patients diagnosed as stage I-II.[1-4]
- A subset of these patients (stage IIB-IIC) are currently eligible for adjuvant therapy; although, it is unclear which of these patients will benefit from and which do not need therapy.[5]
- In the KEYNOTE-716 trial, patients with stage IIB-IIC melanoma treated with pembrolizumab saw a 9% RFS improvement, but 80% had an adverse event (16% ≥grade 3), and 18% discontinued due to adverse events.[5]
- These data emphasize the need for prognostic tools beyond current staging factors to identify patients with the highest and lowest risk of poor outcomes so that patients receive risk-aligned treatment.[1-2]
- The 31-GEP test has been shown in multiple prospective and independent studies to be a consistent and independent predictor of survival outcomes in large populations of patients with stage I-III CM; 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:

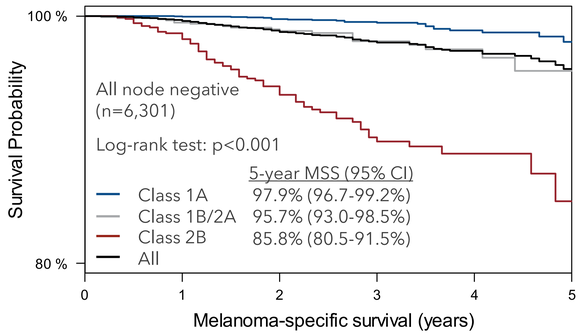
- **Demonstrate the performance of the 31-GEP to identify patients with high-risk tumor biology in an unselected, clinically tested cohort of patients who are node negative.**

Methods

- SEER registries linked individuals diagnosed with CM between 2013-2018 to data for 31-GEP-tested patients (N=9,207 after exclusions). Analysis focused on the subset reported as node negative (N=6,301). Patient 5-year melanoma-specific survival (MSS) was estimated using Kaplan-Meier analysis and the log-rank test. Multivariable Cox regression analysis was used to evaluate significant predictors of melanoma-specific death.

Results

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



- Patients with Class 1A results had higher 5-year MSS than those with Class 1B/2A or Class 2B results.
- The 31-GEP had a sensitivity of 78.4% and a negative predictive value (NPV) of 99.4%.

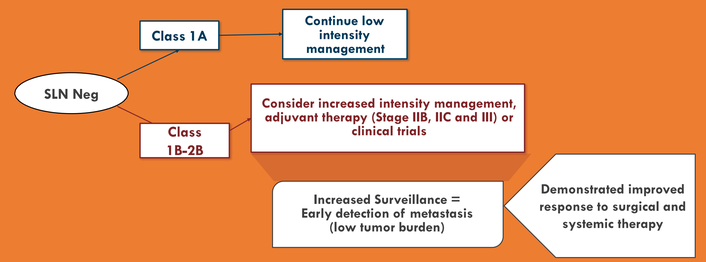
Conclusions

- In a large, unselected cohort of patients with stage I-II CM, the 31-GEP Class 2B result identified patients with a high risk of death from melanoma who should be considered for more aggressive management.
- Conversely, the high NPV suggests that the 31-GEP reliably identifies patients at low risk of tumor progression who could safely avoid intensive surveillance and intervention.

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

Melanoma-specific survival	Multivariable HR	P-value
31-GEP Class 1A	Reference	--
31-GEP Class 1B/2A	1.56	0.232
31-GEP Class 2B	4.08	<0.001
Age (continuous)	1.05	<0.001
Ulceration (negative)	Reference	--
Ulceration (present)	2.10	0.006
Mitotic rate (continuous)	1.02	0.612
Breslow thickness (continuous)	1.16	0.002

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 management decisions.

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