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# Incorporating the 31-gene expression profile test stratifies survival outcomes and leads to improved survival compared to clinicopathologic factors alone: A Surveillance, Epidemiology, and End Results (SEER) Program collaboration

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## Background

The 31-gene expression profile (31-GEP) test for cutaneous melanoma (CM) is a validated risk stratification test that stratifies patients with stage I-III CM into groups at low (Class 1A), intermediate (Class 1B/2A), and high (Class 2B) risk of recurrence, metastasis, and death.<sup>1-7</sup>

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 across the entire staging subgroups.<sup>8-13</sup>

This study provides an analysis of an unselected, prospectively tested patient population showing an impact on outcomes as requested for consideration into national guidelines for CM management.

## Objective

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

- Validate the performance of the 31-GEP for risk stratification in an unselected, prospectively tested cohort.
- Compare survival outcomes between patients tested with the 31-GEP versus patients not tested with the 31-GEP.

## Methods

SEER cancer registries linked CM cases diagnosed from 2013-2018 to data for patients with stage I-III CM tested with the 31-GEP (n=5,226). Linkage was mediated by Information Management Services (an Honest Broker for the SEER registries). A de-identified dataset was used for this analysis.

Kaplan-Meier analysis with the log-rank test was used to analyze patient survival.

To assess if patients tested with the 31-GEP had higher survival rates than non-31-GEP tested patients, a cohort of 31-GEP tested patients (n=3,261) with complete matching data available was matched to a cohort of non-31-GEP tested patients (n=10,863) by 11 covariates in a 1:3 ratio (Table 1). Nearest neighbor matching was performed using the MatchIt package (v.4.3.0) in R (v.4.1.2).

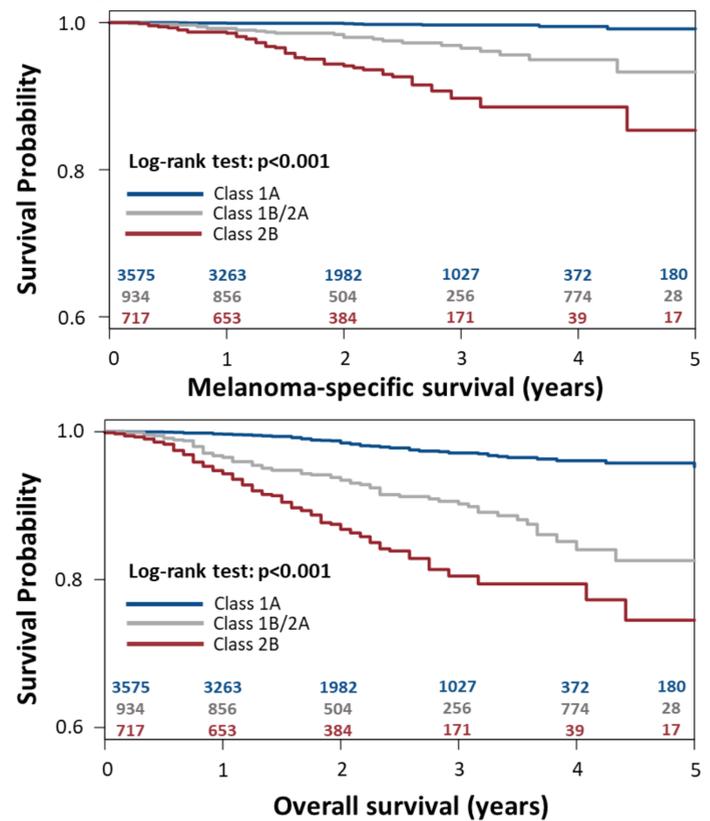
Matching cases were limited to diagnosis in 2016 and forward, controlling for potential access to adjuvant therapy for eligible patients according to national guidelines.

**Table 1. Successful matching of a cohort of non-31-GEP tested patients to the 31-GEP tested population**

Covariates	31-GEP Tested (n=3,621) vs. Non-31-GEP Tested (n=10,863)
Age (median)	p=0.607
Follow-up time (median)	p=0.474
T-stage	p>0.999
Year of diagnosis (2016-2018)	p=0.327
Sex	p=0.199
Yost index (quintile)	p=0.888
SLN assessment	p=0.813
SLN positivity	p=0.757
Mitotic rate (median)	p=0.524
Primary tumor location	p=0.956
Race	p=0.506

## Results

**Figure 1. Risk stratification of patients with stage I-III CM by the 31-GEP (n=5,226)**



Patients with a Class 1A result (blue) had higher MSS (top) and OS (bottom) than patients with a Class 2B result (red).

**Table 2. Multivariable analysis for melanoma-specific and overall survival**

Melanoma-specific survival	Multivariable HR (95% CI)	P-value
<b>31-GEP Class 1B/2A</b>	<b>5.89 (2.57-13.49)</b>	<b>&lt;0.001</b>
<b>31-GEP Class 2B</b>	<b>8.51 (3.58-20.23)</b>	<b>&lt;0.001</b>
Age (continuous)	1.05 (1.03-1.07)	<0.001
Unknown ulceration	1.18 (0.16-8.66)	0.874
Ulceration present	1.46 (0.84-2.53)	0.179
Breslow (continuous)	1.18 (1.08-1.29)	<0.001
SLNB unknown	0.75 (0.36-1.55)	0.439
SLN positive	2.26 (1.30-3.94)	0.004

Overall Survival	Multivariable HR (95% CI)	P-value
<b>31-GEP Class 1B/2A</b>	<b>2.32 (1.63-3.29)</b>	<b>&lt;0.001</b>
<b>31-GEP Class 2B</b>	<b>2.48 (1.65-3.72)</b>	<b>&lt;0.001</b>
Age (continuous)	1.09 (1.07-1.10)	<0.001
Unknown ulceration	0.81 (0.20-3.28)	0.767
Ulceration present	1.39 (1.00-1.93)	0.0504
Breslow (continuous)	1.15 (1.08-1.21)	<0.001
SLNB unknown	1.47 (1.09-1.99)	0.013
SLN positive	1.56 (1.04-2.35)	0.032

SLN: sentinel lymph node. SLNB: sentinel lymph node biopsy. Reference variables include Class 1A for 31-GEP, Ulceration absent for ulceration status, and negative SLNB for SLN status.

**Table 3. Patients with 31-GEP test results had improved survival**

	3-year MSS (95% CI)	Deaths, % (n/N)
31-GEP Tested	97.7% (97.0-98.4%)	1.6% (58/3621)
Matched Untested	96.6% (96.2-97.1%)	2.2% (238/10863)
<b>Hazard ratio<sup>‡</sup></b>	<b>0.73 (0.54-0.97)</b>	<b>P=0.028</b>

	3-year OS (95% CI)	Deaths, % (n/N)
31-GEP Tested	93.1% (92.0-94.2%)	4.8% (174/3621)
Matched Untested	91.2% (90.4-91.9%)	6.1% (658/10863)
<b>Hazard ratio<sup>‡</sup></b>	<b>0.79 (0.67-0.93)</b>	<b>P=0.006</b>

<sup>‡</sup>Hazard ratio (HR) was computed using the matched untested patients as reference for 31-GEP tested cohort.

## Conclusions

- In a large, unselected prospectively tested cohort of patients with stage I-III CM, the 31-GEP stratified patient mortality risk.
- The 31-GEP Class result was a significant and independent predictor of MSS and OS.
- Most important, patients with 31-GEP test results in addition to traditional clinicopathologic factors had improved survival compared to patients with only traditional clinicopathologic factors available to determine their treatment and follow-up plan.

## Acknowledgments & Disclosures

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