31-Gene Expression Profile Testing Survival Benefit in a Population-based Analysis of Cutaneous Melanoma Patients ≥65 Years of Age

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Background

- Risk-stratification determines treatment decisions for patients with cutaneous melanoma (CM), including (a) recommendations on sentinel lymph node biopsy (SLNB) and (b) subsequent management plans including follow-up frequency, imaging-based surveillance, adjuvant therapy, and enrollment in clinical trials. Clinicians have traditionally relied upon clinicopathologic features such as Breslow thickness, and ulceration status.
- The 31-gene expression profile (31-GEP) prognostic test is validated to risk-stratify patients with cutaneous melanoma (CM) into groups at low (Class 1A), intermediate (Class 1B/2A) or high risk (Class 2B) of sentinel-lymph node spread, regional recurrence, distant metastasis, and death and has been shown to be independent of clinicopathologic features.[1-8]
- In clinical use studies, the 31-GEP result changes SLN recommendations, and subsequent management plans are impacted for 1 out of 2 tested patients.[9-14]

Objectives

- To confirm the ability of 31-GEP to risk stratify in a large, unselected, prospectively tested melanoma population.
- To determine the impact of 31-GEP testing on survival outcomes in CM patients 65 years or older compared to a matched cohort of patients not tested with the 31-GEP.

Methods

- **Patient population**: All incident cases of cutaneous melanoma diagnosed between 2013 and 2018 ascertained by the central (state) cancer registries participating in the National Cancer Institute's (NCI) Surveillance Epidemiology and End Results (SEER) Program were included. SEER registries linked their CM cases to 31-GEP testing data provided by the Castle Biosciences. De-identified analytical data set (diagnoses years 2013-2018; test data 2016-2018) was used for this analysis. At the time of the linkage SEER covered 34% of US population. While all cases were included in the linkage, analysis for this study was limited to those cases ≥65 years old at the time of diagnosis and diagnosed in 2016 or later to account for potential access to adjuvant therapy.
- ***Matching the 31-GEP tested patients with an untested patients:*** Nearest neighbor (1-to-3) matching was performed using the MatchIt package (v.4.3.0) in R (v.4.1.2). The selected matching strategy used the shortest distance in multi-dimensional covariate space to determine the best non-GEP-tested matches for each 31-GEP-tested patient. As indicated by p values >0.05, patients were appropriately matched on covariates in **Table 1**.
- ***Statistical analysis:*** Kaplan-Meier analysis, log-rank test, Cox proportional hazards, and parametric regression models were performed to assess the risk differences between 31-GEP classes and 31-GEP tested and non-GEP tested patients. Cox proportional hazards was not violated (p=0.15).

Table 1. Matching of a cohort of non-31-GEP tested patients to the 31-GEP tested population

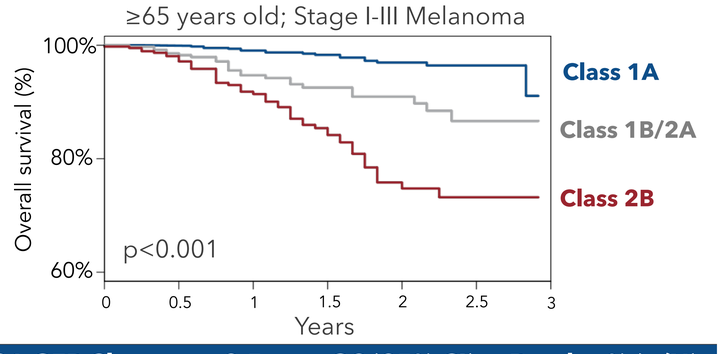
Covariates	31-GEP Tested (n=2048) vs. Non-31-GEP Tested (n=6144)
Age *(median)*	p=0.445
Follow-up time *(median)*	p=0.685
T-stage	p=0.989
Year of diagnosis (2016-2018)	p=0.866
Sex	p=0.560
Mitotic rate *(median)*	p=0.727
County Income *(median)*	p=0.519
SEER Registry	p=0.992
SLN assessment	p=0.999
SLN positivity	p=0.890
AJCC 8th edition	p=0.953
Primary tumor location	p=0.876
Race	p=0.929

Results

- The 31-GEP test stratifies patients with melanoma into low (Class 1A) and high-risk (Class 2B) mortality groups (**Figure 1**).
- When used in conjunction with clinicopathologic features, the 31-GEP guides management decisions in risk-aligned ways for SLNB guidance and surveillance management plans (**Figure 2**).[9-14]
- When controlling for other clinicopathologic variables (**Table 1**), patients tested with the 31-GEP had a better overall survival than patients not tested with the 31-GEP (**Table 2**).
- Collectively, these data provide direct evidence that the 31-GEP test has a beneficial effect on patient survival.

Results

Figure 1. The 31-GEP stratifies patient risk of death in an unselected, prospectively tested population of Medicare-eligible patients



31-GEP Class	2.5-year OS (95% CI)	Deaths, % (n/N)
Class 1A (n=1204)	96.4% (94.6-98.3%)	1.5% (18/1204)
Class 1B/2A (n=436)	86.6% (80.7-93.0%)	5.5% (24/436)
Class 2B (n=408)	73.2% (66.4-80.7%)	12.3% (53/408)

Diagnosis date 2016 and onward.

- Patients with a Class 2B 31-GEP result had a 10-fold increase in death rate compared with patients with a Class 1A result.

Figure 2. Clinical use algorithms for incorporating 31-GEP testing into clinical workflow

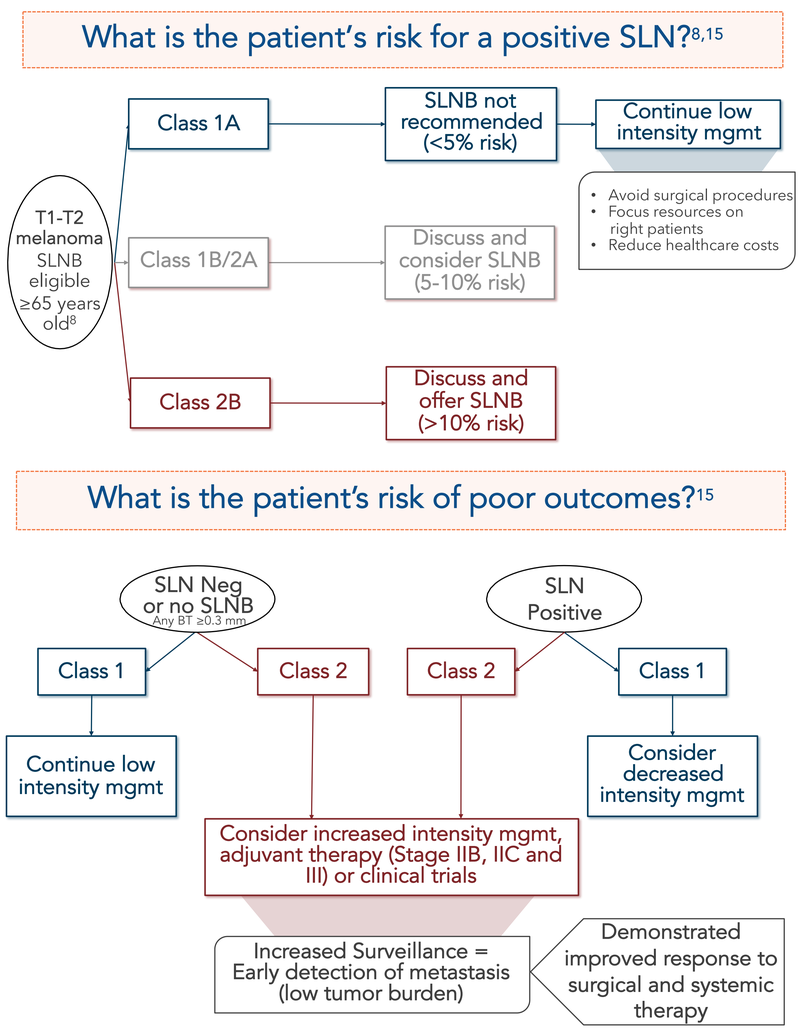


Table 2. Patients receiving 31-GEP test results had improved overall survival compared to those not tested

Group‡	2.5-year OS (95% CI)	Deaths, % (n/N)
31-GEP Tested	89.4% (87.0-91.7%)	4.6% (95/2048)
Matched Untested	84.6% (83.1-86.3%)	7.0% (430/6144)
Hazard ratio	**0.66 (95% CI 0.53-0.82)**	**P=0.002**

MSLT-1 Group†	5-year MSS (SE)	Deaths, % (n/N)
SLNB + WLE	86.6% (1.3)	16.2% (125/770)
WLE	85.7% (1.6)	19.4% (97/500)
Hazard Ratio	0.84 (95% CI 0.64-1.09)	P=0.18

‡Hazard ratio (HR) was computed using the untested patients as reference for 31-GEP testing. An HR less than 1.0 demonstrates improved survival in 31-GEP tested patients. Diagnosis date 2016 and onward. †MSLT-1[16]: Multicenter Selective Lymphadenectomy Trial-1. SLNB: sentinel lymph node biopsy. WLE: wide local excision. SE: standard error. †Intermediate thickness tumors (1.2-3.5 mm).

- In contrast to the prognostic SLNB (as reported in MSLT-I[16]), patients tested with the 31-GEP received a survival benefit compared to patients not tested with the 31-GEP test.

Conclusions

- Consistent with previously published studies, the 31-GEP risk Classes were associated with significantly different overall survival in this large, population-level study.
- Medicare-eligible patients prospectively tested with the 31-GEP had improved overall survival compared to clinically and demographically, untested patients, providing direct evidence of the beneficial effect of 31-GEP testing.
- Incorporating 31-GEP testing into clinical practice can aid risk-aligned management decisions, thereby improving patient outcomes and survival.

References

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Disclosures

- CNB, BJM, JJS, SJK, and KRC are employees and shareholders of Castle Biosciences, Inc. VIP has no conflicts of interest.

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