Integrating the 31-gene expression profile and clinicopathologic data to determine the risk of sentinel lymph node positivity and recurrence-free survival in cutaneous melanoma

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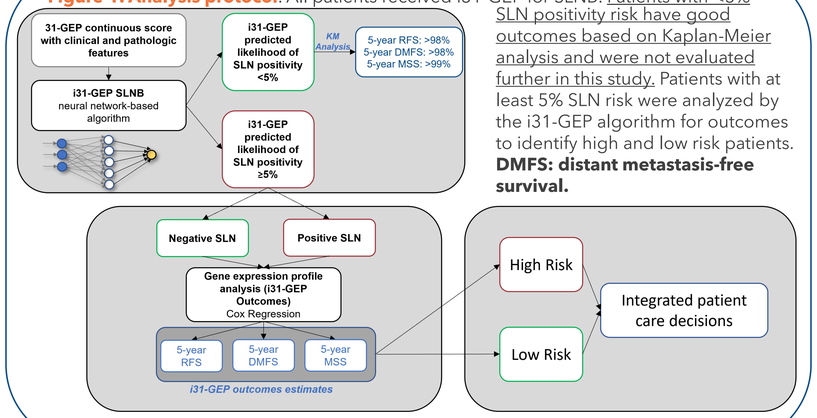
Background

- The 31-gene expression profile (31-GEP) test for cutaneous melanoma assesses the risk of **sentinel lymph node biopsy (SLNB)** positivity and regional recurrence, distant metastasis, and **melanoma-specific survival (MSS)** using the primary tumor genetic profile.[1-10]
- SLNB has a more than 80% negativity rate, and many patients with a negative SLNB experience disease recurrence or death.[11,12]

Objective

- The purpose of this study was to demonstrate the combined ability of two independently validated algorithms that incorporate the 31-GEP with clinicopathologic features to predict individual SLNB positivity risk and **recurrence-free survival (RFS)**.

Figure 1. Analysis protocol. All patients received i31-GEP for SLNB. Patients with <5% SLN positivity risk have good outcomes based on Kaplan-Meier analysis and were not evaluated further in this study. Patients with at least 5% SLN risk were analyzed by the i31-GEP algorithm for outcomes to identify high and low risk patients. **DMFS: distant metastasis-free survival.**

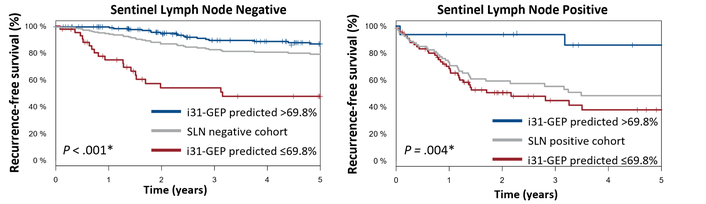


Methods

- Using artificial intelligence techniques, an algorithm to determine the individual likelihood of SLN positivity was developed from 1398 cases and validated in an independent cohort of 1674 cases (i31-GEP-SLNB). Next, a separate algorithm for personalized survival predictions for RFS, DMFS, and MSS was developed from 1581 cases and validated in an independent cohort of 523 cases (i31-GEP-outcomes). Based on the available data, 98% of patients in the validation cohort did not receive PD-1, CTLA-4, or BRAF/MEK adjuvant therapy.
- To create risk cut-points that align with NCCN treatment recommendations, the midpoints between stage IIA and IIB was set as the risk cut-off (RFS: 69.8%; DMFS: 82.6%). Those with an i31-GEP-outcomes predicted RFS or DMFS higher than the cut-off were classified as low risk. Otherwise, they were classified as high risk.
- To evaluate the prognostic value of using both i31-GEP algorithms, the subset of patients (N=433) not utilized in the development of either algorithm was analyzed first by i31-GEP-SLNB, followed by i31-GEP-outcomes.

Results

Figure 2. Five-year RFS for patients stratified by i31-GEP risk groups in SLN negative and positive patient populations.



GROUP	5-year RFS (95% CI)	Recurrences, % (n/N)
Low Risk; >69.8% (n=172)	86.7% (81.2-92.7%)	10.5% (18/172)
SLN negative cohort (n=215)	79.2% (73.4-85.5%)	17.7% (38/215)
High Risk; ≤69.8% (n=43)	47.7% (33.6-67.7%)	46.5% (20/43)

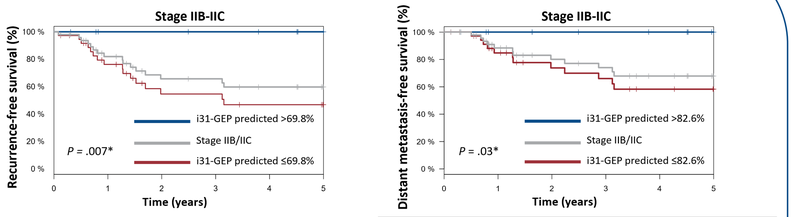
*comparison between i31-GEP low and high risk.

GROUP	5-year RFS (95% CI)	Recurrences, % (n/N)
Low Risk; >69.8% (n=16)	85.9% (69.5-100%)	18.8% (3/16)
SLN positive cohort (n=83)	48.7% (37.6-63.1%)	45.8% (38/83)
High Risk; ≤69.8% (n=67)	37.9% (25.8-55.6%)	52.2% (35/67)

*comparison between i31-GEP low and high risk.

- Data includes only patients with at least 5% SLN positivity risk by i31-GEP SLNB (n=298),
- DMFS (not shown) was also significantly stratified by the i31-GEP for outcomes.

Figure 3. Five-year RFS and DMFS for patients with stage IIB-IIC disease.



GROUP	5-year RFS (95% CI)	Recurrences, % (n/N)
Low risk; >69.8% predicted (n=12)	100% (100-100%)	0% (0/12)
Stage IIB/IIC (n=49)	59.7% (46.0-77.6%)	34.7% (17/49)
High Risk; ≤69.8% predicted (n=37)	46.8% (31.6-69.4%)	45.9% (17/37)

*comparison between i31-GEP low and high risk.

GROUP	5-year DMFS (95% CI)	Distant Metastases, % (n/N)
Low Risk; >82.6% predicted (n=12)	100% (100-100%)	0% (0/12)
Stage IIB/IIC (n=49)	67.9% (54.2-85.0%)	26.5% (13/49)
High Risk; ≤82.6% predicted (n=37)	58.3% (42.5-79.9%)	35.1% (13/37)

*comparison between i31-GEP low and high risk.

- Data taken from total cohort (N=433). All patients with stage IIB-IIC disease received higher than 5% SLN positivity risk by the i31-GEP for SLNB.

Conclusions

- The i31-GEP for SLNB identified 31.2% (135/433) of patients with a <5% likelihood of SLN positivity and these patients had high survival rates, showing that these patients could safely forego SLNB.
- In the SLN negative population, 20% of patients identified as high risk by the i31-GEP result and had 5-year RFS rates that were identical to patients with stage III disease (47.7% vs. 48.7%, respectively).
- Overall, using NCCN treatment recommendations, the i31-GEP test identified **44.8% (194/433)** of patients who could have **avoided SLNB** or were **re-stratified** as low or high risk compared to SLN status alone.
- The i31-GEP can stratify patients with **stage IIB-IIC melanoma** according to risk of recurrence or distant metastasis.
- Using the combined i31-GEP integrated approach can identify patients who may potentially forego SLNB and those with high and low risk of recurrence for more **personalized patient care decisions**.

References

1. Gerami, P. *et al. Clin Cancer Res 2015.* **21** *(1) 175-183*
2. Keller, J. *et al. Cancer Med* 2019. **8** (5) 2205-2212.
3. Zager, J. *et al. BMC Cancer* 2018. **18** (1) 130.
4. Whitman, E. *et al. JCO PO* 2021. (5) 1466-1479.
5. Hsueh, E. *et al. JCO PO* 2021. **5** 589-601.
6. Podlipnik, S. *et al. JEADV* 2019. **33** (5) 857-862.
7. Arnot, S. *et al. AJS* 2021.
8. Dillon, L. *et al. SKIN* 2018. **2** (2) 111-121.
9. Gastman, B. *et al. JAAD* 2019. **80** (1) 149-157.e4.
10. Gastman, B. *et al. Head & Neck* 2019. **41** (4) 871-879.
11. Chen, J. *et al. Oncotarget* 2016. **7** (29) 45671-45677.
12. Morton, D. *et al. NEJM* 2014. **370** (7) 599-609.

Acknowledgments & Disclosures

- We would like to thank the patients and clinicians who received test results through Castle.
- This study was sponsored by Castle Biosciences, Inc.
- BM, AQ, CB, and KC are employees and shareholders of Castle Biosciences, Inc.. EW and JV are on the speaker's bureau for Castle Biosciences, Inc. NT has no conflicts.

Presented at the 2021 Fall Clinical Dermatology Conference in Las Vegas, NV; October 21-24, 2021.