In a prospective, multicenter study, the 31-GEP identified patients at increased risk of tumor recurrence and added significant prognostic value to AJCC staging

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Background

- Cutaneous melanoma (CM) guidelines base management decisions on a patient's American Joint Committee on Cancer (AJCC) tumor stage.[1,2]
- Limitations in staging accuracy suggest additional tools could improve risk-aligned patient management decisions.[3-6]
- The 31-gene expression profile (GEP) test identifies patients with CM with low (Class 1A), intermediate (Class 1B/2A), or high (Class 2B) risk for sentinel lymph node (SLN) positivity, recurrence, metastasis, and death.[7-9]

Objective

- **Prospectively validate the 31-GEP for risk of recurrence and demonstrate the added value of 31-GEP to AJCC staging.**

Methods

- Patients were included in the prospective CONNECTION study if they were tested with the 31-GEP from 2018 onward (n=878). Survival was estimated using Kaplan-Meier analysis and 31-GEP stratification tested with the log-rank test. Cox regression was performed to identify predictors of recurrence. ANOVA was used to compare Cox models for the most accurate recurrence prediction.

References

1. Gershenwald JE, et al. AJCC cancer staging manual. 8th Edition. 2017. 2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), Cutaneous Melanoma 2024. 2024. 3. Garbe C, et al. JCO. 2022. 4. Barreiro-Capurro A, et al. European Journal of Cancer 2021. 5. Weitemeyer MB, et al. J Surg Oncol 2022. 6. Helvind NM, et al. JAMA Dermatology 2023. 7. Bailey CN, et al. JCO Precis Oncol 2023. 8. Vetto JT, et al.Future Oncol. 2019. 9. Jarell A, et al. Future Oncol 2021.

Results

Table 1. Patient demographics

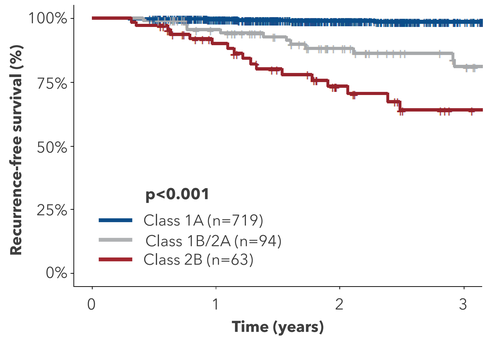
Factor	N=878	Rec Events
Age, median (rage)	63 (19-90)	
Ulceration, % (n)	9.4% (75)	
Breslow, mm range (median)	0.5 (0.1-18.0)	
Mitotic rate, (per/mm^2) range (median)	1 (0-26)	
SLN status, % (n)		
Negative	26.0% (228)	23
Positive	4.3% (38)	10
Unknown	69.6% (610)	7
31-GEP result, % (n)		
Class 1A	82.1% (719)	10
Class 1B	5.3% (46)	4
Class 2A	5.5% (48)	9
Class 2B	7.2% (63)	17
AJCC Stage		
Stage I	87.1% (763)	14
Stage II	8.6% (75)	16
Stage III	4.3% (38)	10
T-stage		
T1	78.2% (685)	8
T2	15.0% (131)	19
T3	4.7% (41)	5
T4	2.2% (19)	8

Table 2. Multivariable analysis demonstrates independent and significant prognostic information

Factor	Hazard ratio (95% CI)
Class 1A	Reference
Class 1B/2A	**3.12 (1.07-9.05)***
Class 2B	**5.91 (1.94-18.03)***
Stage IA	Reference
Stage IB	**4.02 (1.24-12.99)***
Stage IIA	**6.06 (1.68-21.85)***
Stage IIB	4.63 (0.96-22.34)
Stage IIC	**17.14 (3.23-91.13)***
Stage III	**8.84 (2.46-31.83)***

*Indicates statistical significance (p<0.05).

Figure 1. The 31-GEP stratifies recurrence risk in prospectively tested patients.



Group	3-year RFS (95% CI)
Class 1A (n=719)	98.5% (97.5-99.6%)
Class 1B/2A (n=94)	80.8% (71.0-92.0%)
Class 2B (n=63)	63.0% (49.8-79.8%)

Patients with a Class 1A result had **significantly higher 3-year recurrence-free survival** than those with a Class 1B/2A or Class 2B result (p<0.001).

Table 3. Adding the 31-GEP to AJCC staging improves risk stratification over AJCC staging alone

Group	Likelihood ratio
31-GEP	71.52
AJCC staging	75.57
31-GEP + AJCC	**86.15***

*Indicates statistical significance (p<0.05). ANOVA p=0.005

Comparing AJCC staging alone to 31-GEP+AJCC showed that **adding 31-GEP to AJCC significantly improved recurrence prediction accuracy** (ANOVA: $\chi 2$=9.50, p=0.005).

Clinical Impact

- The 31-GEP identifies patients at high risk of recurrence who should be managed more intensely.
- Adding 31-GEP to staging allows better risk-aligned care decisions, which can lead to improved patient outcomes.

Conclusions

- In this prospective study, the 31-GEP stratified risk of recurrence, was a significant predictor of recurrence, and added significant predictive value to AJCC staging.

Acknowledgments & Disclosures

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