The integrated 31-gene expression profile (i31-GEP) test for cutaneous melanoma outperforms a clinicopathologic-only nomogram at identifying patients who can safely forego sentinel lymph node biopsy.

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Background

- National Comprehensive Cancer Network (NCCN) guidelines recommend forgoing sentinel lymph node biopsy (SLNB) if the population-based point-estimate risk of positivity is <5% (T1a with no high-risk features), discuss and consider SLNB if the risk is 5-10% (T1a with high-risk feature(s), T1b), and recommend SLNB if the risk is >10% (T2-T4).[1]
- As it relates to guiding SLNB recommendations, clinicians know that using T-stage provides a broad bin for recommendations, but the precision of these population-based point estimates has generally not been published.
- Novel tools have been developed to improve SLNB recommendations. Most recently, the integrated 31-gene expression profile (i31-GEP) which combines the 31-GEP with clinical and pathological factors was developed to identify patients who can safely forego SLNB and also provides risk of recurrence outcomes.[3-10] Separately, the Melanoma Institute of Australia (MIA) developed a nomogram using only clinical and pathological features, some of which were not included in the i31-GEP.[11-12] Most importantly, the MIA model does not include genomic evaluation of the melanoma (Table 1).

Table 1: Variables included in i31-GEP test or MIA Model

Potential Prediction Variables	Included in i31-GEP Test	Relative Importance*		Included in MIA Model	Relative Importance**
31-GEP continuous score	√	**91.3**	**P<.001**		
Breslow thickness	√	53.5	P<.001	√	1.75 (per mm)
Mitotic Rate	√	20.7	P<.001	√	1.89-2.47 (1-4+/mm^2)
Ulceration	√	19.1	P<.001	√	1.32 (presence)
Age	√	10.5	P=.001	√	0.97 (per year)
TILS					
LVI				√	4.31 (presence)
Microsatellites					
Sex					
Histopathologic subtype				√	0.06– 2.15 (pure desmoplastic-acral)
Transected bases					
Tumor Site					
Regression					

*Log-likelihood value (G2); reported in Whitman et al. 2021.
**Odds ratio; reported in Lo et al. 2020

Methods

For patients with T1aHR-T2 cutaneous melanoma (n=582),[3] we compared the i31-GEP profile the MIA nomogram in patients with T1a-HR – T2 melanomas. Precision was evaluated using 95% CIs for the MIA and the i31-GEP. MIA 95% CIs obtained directly from the online calculator. i31-GEP 95% CIs obtained using a Lowess spline.

References

1. National Comprehensive Cancer Guidelines, v2, 2022. 2. Chen et al. *Oncotarget*. 2016. 3. Whitman et al. *JCO PO* 2021. 5. Vetto et al. *Future Oncology*. 2019. 6. Hsueh et al. *JCO PO* 2021. 7. Jarell et al. *JAAD*. 2022. 8. Arnot et al. *AJS*. 2021. 9. Dillon et al. *CMRO*.2022. 10. Ahmed et al. *Cancer Med*. 2022. 11. Lo et al. *JCO* 2020. 12. El Sharouni et al. *BJD*. 2021. 13. Vickers et al. *BMJ*. 2016. 14. Vickers et al. *Diagn Progn Res*. 2019.

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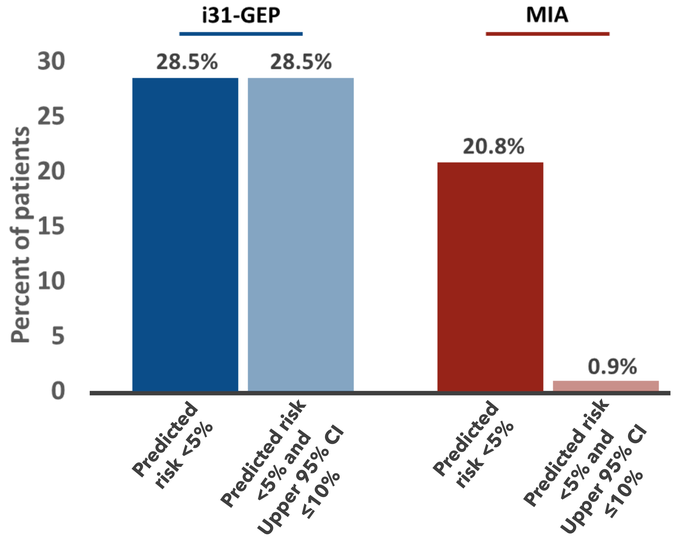
Clinical Issue and Aim

To make evidence-based decisions about performing SLNB, clinicians should have confidence that patients predicted to have <5% risk by a model are truly low-risk based on the model's precision, measured by 95% CIs that do not cross clinically relevant decision thresholds.

To answer this clinical question, we evaluated the i31-GEP and subsequently compared it to the Melanoma Institute of Australia (MIA) developed nomogram model.

Figure 1. Comparing point-estimate and 95% CIs for i31-GEP and MIA model and i31-GEP (T1aHR-T2)



- MIA identified 20.8% (121/582) of patients as having <5% positivity risk, but just 0.9% (5/582) of patients had <5% risk with upper 95% CIs ≤10%, casting doubt on the ability of the MIA nomogram to provide precise, actionable, risk assessment.
- The i31-GEP identified 28.5% (166/582) of patients as having <5% positivity risk with 100% (166/166) of the upper 95% CIs being ≤10%, indicating confidence in the i31-GEPs ability to provide actionable risk estimates.

Table 2. Reclassification of risk in patients with 5-10% risk (T1aHR-T1b tumors) for whom guidance is not definitive.

Test	NCCN risk	Reclassified as <5% risk, % (n/N)	Reclassified as >10% risk, % (n/N)	Total reclassified, % (n/N)
i31-GEP	**5-10% risk (T1aHR-T1b), N=284**	**49.6% (141/284)**	**10.6% (30/284)**	**60.2% (171/284)**
MIA		**1.4% (4/284)**	**12.3% (35/284)**	**13.7% (39/284)**

- Patients are included in the <5% risk category when the upper 95% CI is also ≤10%. Patients are included in the >10% risk category when the lower 95% CI is also ≥5%.

Summary & Conclusions

- Actionability requires precision, defined here as confidence in a risk prediction of SLN+ below the threshold (≤10%) where SLNB is recommended to be 'offered'.
- All patients identified as having <5% risk by the i31-GEP had upper 95% CIs ≤10%; meaning none of these patients would have been 'offered' an SLNB under current guidelines.
- In contrast, using the MIA nomogram, only 0.9% of the entire cohort had an SLN+ risk <5% with 95% CI ≤10%, suggesting lack of confidence in the estimate of risk and, thus, in the decision to forgo the SLNB.
- Separately, in a previously published cohort (n=433), patients that had an i31-GEP predicted SLN positivity risk <5% had a 5-year distant metastasis free survival rate of >98%,[7] an outcome not reported by this MIA nomogram.
- In this multi-center cohort of 582 patients, the i31-GEP was superior to MIA in identifying T1aHR-T2 patients who could avoid SLNB. Furthermore, the i31-GEP identified more patients traditionally thought to have a 5-10% risk (T1aHR-T1b tumors) who had <5% risk (141 vs. 4) and could forego SLNB.

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