

Comparing Two Gene Expression Profile Tests to Standard of Care for Identifying Patients With Cutaneous Melanoma at Low Risk of Sentinel Lymph Node Positivity

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Abstract

Background/Aim: The National Comprehensive Cancer Network (NCCN) Guidelines for cutaneous melanoma (CM) recommend avoiding sentinel lymph node biopsy (SLNB) when the positivity risk is <5%, considering SLNB when the risk is 5-10%, or offering SLNB when the risk is >10%. Most patients undergoing SLNB have a negative result, showing that reliance upon the American Joint Committee on Cancer (AJCC) T-stage alone results in most patients undergoing an unnecessary, negative, unreliable, invasive procedure.

Materials and Methods: Two gene expression profile (GEP) tests, the CP-GEP and the 31-GEP, have been developed to identify patients at low risk of SLN positivity who may consider avoiding SLNB. We analyzed the accuracy of the CP-GEP and 31-GEP in identifying patients with <5% risk of SLN positivity across the five validation studies of the CP-GEP and four validation studies of the 31-GEP in T1-T2 tumors.

Results: Patients considered low risk by the CP-GEP had an SLN positivity rate of 6.2%, higher than the risk threshold of 5% used by the NCCN to guide SLNB decisions. In contrast, patients considered low risk by the 31-GEP or i31-SLNB had a 2.8% SLN positivity rate, a substantial improvement over AJCC-staging guidance.

Conclusion: Overall, the CP-GEP did not perform as well as AJCC, while the 31-GEP performed better than AJCC.

Keywords: Melanoma, prognosis, gene expression profile, 31-GEP, CP-GEP.

Introduction

The American Joint Committee on Cancer (AJCC) uses staging criteria that include Breslow thickness, tumor ulceration, sentinel lymph node (SLN) status, and the

presence and location of tumor metastases to estimate a patient's risk of dying from cutaneous melanoma (CM) (1). SLN biopsy (SLNB) is a prognostic tool for identifying patients with a high risk of dying from their disease. A positive SLN directly affects risk-based management



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decisions, specifically eligibility for potentially life-saving adjuvant therapies.

The National Comprehensive Cancer Network (NCCN) Guidelines for Cutaneous Melanoma (CM) recommend avoiding SLNB when the sentinel node positivity risk is <5% (T1a tumors with no high-risk factors). Patients should either consider or undergo SLNB when the risk is 5-10% or >10%, respectively (2). The 5% risk threshold means that when avoiding SLNB decision-making using staging criteria alone, one positive SLN would be missed for every 20 patients who avoid SLNB, *i.e.*, a 19:1 true-to-false negative ratio (TN:FN ratio). Patients with T3-T4 tumors have higher rates of SLN positivity, making the decision to undergo SLNB clear. However, over 90% of patients with T1-T2 tumors will have a negative node (3), and in those with thin tumors the likelihood of complications from the procedure exceeds the likelihood of having a positive node (4). Thus, there is a particular unmet need for patients with T1-T2 tumors in predicting which patients are most likely to have a positive node and need to undergo the procedure, and which patients have <5% risk and can safely avoid SLNB. Further, T1-T2 tumors account for most (~75%) newly diagnosed melanoma; thus, this is relevant to most newly diagnosed patients (5). Accurate prognostic tools that clearly meet or exceed well-established thresholds for clinical utility are needed to identify patients who can safely forego SLNB and are at low risk of recurrence after avoiding SLNB to spare patients from unnecessary surgery and complications and significant healthcare costs.

Gene expression profile (GEP) tests use gene expression levels to calculate a tumor's molecular risk level for outcomes such as sentinel node, distant metastases, or disease mortality. GEP tests have the potential to add valuable additional risk information when used with current staging systems. A useful GEP test should provide clinical utility in guiding SLNB decisions, and it must provide independent and accurate risk assessment. Patients who forego the procedure due to the GEP result must not have poor outcomes. The 31-GEP test has been previously validated to provide significant risk stratification of

recurrence, metastasis, and melanoma-specific mortality (6). Studies have shown the 31-GEP consistently provides significant prognostic prediction independent of clinical and pathological factors in univariate and multivariable analyses (6-9). Additionally, studies have found that adding 31-GEP results to AJCC staging improved prognostic accuracy compared to using AJCC staging alone (10). More recently, distinct algorithms incorporating the 31-GEP result with clinical and pathological features have been validated to provide a precise risk of SLNB positivity (i31-SLNB) and risk of recurrence (i31-ROR) (11, 12). The i31-SLNB and i31-ROR algorithms were developed using different computational methods (a neural network algorithm and a Cox regression model, respectively), and the clinicopathological factors that contributed to the algorithms differed (Breslow thickness, mitotic rate, and age for i31-SLNB and age, Breslow thickness, mitotic rate, N-category, ulceration, and tumor location for the i31-ROR) (11, 12). In the present analysis, we identified four studies focused on validating the performance of 31-GEP/i31-SLNB risk prediction to calculate false omission rates in the T1-T2 population, where SLNB decision-making is most difficult and where additional prognostic information regarding SLN positivity can provide the most value (13-15).

The CP-GEP test combines clinicopathological (CP) factors (Breslow thickness and age) with GEP of 8 genes to predict a patient's risk of SLN positivity as high or low (16). Recent data have explored whether the CP-GEP can predict a patient's prognosis for recurrence; however, the test was not developed to assess recurrence risk prediction (17). We identified five studies that focused on validating the performance of CP-GEP for SLNB risk prediction and enabled calculation of false omission rates in the T1-T2 population (16, 18-21). However, previous independent analyses indicated that the CP-GEP test did not perform better or add value beyond using CP factors alone (22, 23). In this analysis, we compared the performance of the CP-GEP and 31-GEP/i31-SLNB tests to the NCCN standard of 19:1 TN:FN ratio (*i.e.*, 5% false omission rate) for the accurate identification of patients who can safely avoid SLNB.

Table I. Performance of the CP-GEP and 31-GEP tests to identify true negative sentinel lymph node biopsies in patients with T1-T2 tumors classified as low risk by GEP testing.

GEP test	TN:FN ratio ^a	FO rate	Reference
CP-GEP			
T1-T2	12:1	7.9%	Mulder <i>et al.</i> , 2020 (18)
T1-T2	27:1	3.5%	Johansson <i>et al.</i> , 2021 (19)
T1-T2	15:1	6.3%	Yousaf <i>et al.</i> , 2021 (20)
T1-T2	27:1	3.5%	Stassen <i>et al.</i> , 2023 (21)
T1-T2	14:1	6.8%	Sondak <i>et al.</i> , SMR 2024 (34)
CP-GEP T1-T2 Overall	15:1	6.2%	
31-GEP/i31-SLNB			
T1-T2 (31-GEP)	34:1	3.0%	Yamamoto <i>et al.</i> , 2023 (13)
T1-T2 (i31-SLNB) ^b	25:1	3.9%	Whitman <i>et al.</i> , 2021 (11)
T1-T2 (i31-SLNB)	30:0	0%	Kriza <i>et al.</i> , 2024 (14)
T1-T2a (i31-SLNB)	58:0	0%	Beard <i>et al.</i> , ECD0 2024 (24)
31-GEP/i31-SLNB T1-T2 Overall	34:1	2.8%	

GEP: Gene expression profile; TN:FN ratio: true negative to false negative ratio; FO rate: false omission rate; 31-GEP: 31-gene expression profile; i31-SLNB: integrated 31-GEP test for sentinel lymph node biopsy prediction; SMR: Society for Melanoma Research; ECD0: European Congress on Dermato-Oncology. ^aBold indicates that the TN:FN ratio was the same or worse than using standard clinicopathologic features (19:1). For calculations, negative was defined as “low risk” by CP-GEP, Class 1A for 31-GEP, and <5% risk of SLN positivity by i31-SLNB. ^bThe current analysis includes only data from the original development and validation of the i31-SLNB (Whitman *et al.*, 2021) for patients who underwent SLNB (11).

Materials and Methods

We calculated the TN:FN ratios for patients with T1 and T2 tumors included in five reported validation cohorts using the CP-GEP, one cohort using the 31-GEP, and three cohorts using the i31-SLNB (Table I). For the CP-GEP, Mulder *et al.* included a cohort of 210 patients (T1-T2=105), Johansson *et al.* included 421 patients (T1-T2=240), Yousaf *et al.* included 208 patients (T1-T2=153), Stassen included 260 patients (T1-T2=186), and Sondak *et al.* included 1,686 patients (T1-T2=1,345). For the 31-GEP, Yamamoto *et al.* included a cohort of 193 patients (T1-T2=193). For the i31-SLNB, Whitman *et al.* included a cohort of 1,258 patients (896 T1-T2), Kriza *et al.* included a cohort of 156 patients (T1-T2=91), and Beard *et al.* included a cohort of 471 patients (T1-T2a=471) (11, 13, 14, 24).

We compared the TN:FN ratio and false omission rates calculated for patients considered low risk by the CP-GEP or 31-GEP/i31-SLNB tests to that based on staging (*i.e.*, 5% false omission rate or 19:1 TN:FN ratio) (18-21). A ratio less than 19:1 or false omission rate $\geq$ 5% indicated the test performed worse than current staging, and a test

with a ratio greater than 19:1 or false omission rate <5% indicated it performed better than staging at identifying patients who could safely avoid SLNB. A Chi-squared test was used to test for significant difference in the false omission rates, with $p < 0.05$ as statistically significant.

Results

In T1-T2 tumors, the calculated TN:FN ratio for the CP-GEP test was 12:1 (7.9% false omission rate) in Mulder *et al.*, 27:1 (3.5% false omission rate) in Johansson *et al.*, 15:1 (6.3% false omission rate) in Yousaf *et al.*, and 27:1 (3.5% false omission rate) in Stassen *et al.* (Table I) (18-21). The most recent data from a large, multi-center U.S.-based prospective study (MERLIN_001) found a 14:1 ratio (6.8% false omission rate) among the T1-T2 patients. Calculating the overall weighted-average performance from these studies resulted in an overall ratio of 15:1 (6.2% false omission rate) for the CP-GEP test in this population, which is inferior to AJCC staging to rule-out an SLNB.

Next, we analyzed the ratio for the 31-GEP/i31-SLNB test in T1-T2 tumors. The calculated TN:FN ratio was 34:1

(3.0% false omission rate; 31-GEP) in Yamamoto *et al.* (13), 25:1 (3.9% false omission rate, i31-SLNB) in Whitman *et al.* (11), and 30:0 (0% false omission rate; i31-SLNB) in Kriza *et al.* (14). The most recent data from a large multi-center U.S.-based prospective study found a 58:0 ratio (0% false omission rate; i31-SLNB) (24). Calculating the overall weighted-average performance from these studies resulted in an overall ratio of 34:1 (2.8% false omission rate) for the 31-GEP/i31-SLNB test in this population, which is superior to standard of care AJCC staging. Chi-squared analysis comparing the false omission rates of CP-GEP to the 31-GEP/i31-SLNB found that the 31-GEP/i31-SLNB had a significantly lower false omission rate than CP-GEP ($p=0.012$).

Discussion

The *post-hoc* analysis showed that the CP-GEP performance provides less accurate predictions of sentinel node positivity than T-stage alone for identifying patients with T1-T2 melanoma with a <5% risk of having a positive SLNB. By contrast, the 31-GEP/i31-SLNB test outperforms T staging alone. The low-risk CP-GEP group in the studies had a mean 6.2% false omission rate. In contrast, the 31-GEP had a false omission rate of 3% and the i31-SLNB had a false omission rate of 0% in two studies. These data show that the CP-GEP does not add additional prognostic information to help identify patients at low risk of SLN positivity, while the 31-GEP and i31-SLNB allow for risk stratification that exceeds that of AJCC staging alone.

SLN positivity risk-based decisions have traditionally been determined using only clinicopathologic factors, including Breslow thickness, ulceration, mitotic rate, tumor location, lympho-vascular invasion, and age (2). In addition to AJCC staging, several nomograms based on different clinicopathologic factors have been developed to try to improve SLN prediction, but these tools have not been assessed in prospective studies and have not demonstrated a benefit over standard AJCC staging for predicting SLN positivity (25-27). Furthermore, several different GEP tools have been developed to predict if a

patient is likely to have a positive SLN or is at low risk and can safely avoid SLNB. In the present analysis, we found that one test, the CP-GEP, did not outperform staging in identifying patients with a low risk of SLN positivity. This is perhaps unsurprising given that no studies have found that the gene expression data included in the CP-GEP test provide additional independent prognostic information to the clinicopathologic factors; therefore, it is unknown if the gene expression data included in the algorithm provide any improvement over AJCC staging in SLNB prediction accuracy. In contrast, the 31-GEP/i31-SLNB, did perform better than AJCC staging. These findings are consistent with previous studies that show the 31-GEP and i31-SLNB improve SLNB and risk prediction accuracy compared with AJCC staging and that they more accurately predict SLN positivity than nomograms that only include clinicopathologic factors (*i.e.*, MSKCC and MIA SLNB prediction nomograms) (10-12).

A recent study sought to assess an additional utility for the CP-GEP test in predicting the risk of recurrence. Patients with high-risk CP-GEP results had lower recurrence-free survival (RFS) rates than those classified as low risk by the test; although, an online nomogram using CP factors alone provided better risk stratification (17). The study authors concluded that the current CP-GEP test did not provide precise and accurate enough information to be introduced into clinical practice as a risk stratification tool for recurrence (17). Furthermore, Eggermont *et al.* published a report showing that in patients with a low-risk CP-GEP result who had a positive SLN (*i.e.*, false negative), 5-year recurrence-free survival was 68%, suggesting that had CP-GEP been used to guide care, these patients would have been considered low risk when they were actually at high risk of recurrence (28).

In contrast, the 31-GEP and i31-SLNB consistently provided improved SLNB risk prediction compared with AJCC staging alone. The combined 31-GEP/i31-SLNB TN:FN ratio was 34:1 (2.8% false omission rate), an improvement over AJCC staging. Further, a follow-up study of low-risk (Class 1A) patients who avoided SLNB found no recurrences with a median follow-up of 2 years (29). In

addition, multiple prospective studies have demonstrated that the 31-GEP stratifies risk of recurrence, metastasis, and death (30-32), and two studies have shown that patients who received the 31-GEP test as part of their clinical care had higher survival rates than patients who did not receive 31-GEP testing 9,33. Thus, the current analysis adds to the evidence that the 31-GEP provides personalized risk information, allowing clinicians and patients to make risk-appropriate management and treatment decisions, associated with improved patient outcomes. This analysis also shows that the 31-GEP/i31-SLNB is superior to the performance of the CP-GEP. Limitations of this analysis include the relatively small number of patients in the different study subsets and the challenges of comparing results across different studies.

In summary, the analyses reported here indicate that the CP-GEP does not perform better than AJCC staging for identifying patients at low risk of SLN positivity and should not be used to guide patient management. In contrast, the 31-GEP and i31-SLNB improve SLNB decision-making in patients with T1-T2 tumors over AJCC staging and can help provide better risk-aligned patient management decisions.

Conflicts of Interest

JMG is on the Speaker's Bureau for Castle Biosciences, Inc. PAP is a consultant for Castle Biosciences, Inc. LKF has no conflicts to declare.

Authors' Contributions

PAP, LKF, and JMG approved the study design and analysis. PAP, LKF, and JMG edited, reviewed, and approved the final version of the manuscript.

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