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Clinical evaluation of the clinicopathologic and gene expression profile (CP-GEP) in patients with melanoma eligible for sentinel lymph node biopsy: A multicenter prospective Dutch study

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ABSTRACT

Sentinel lymph node biopsy (SLNB) is recommended for patients with >pT1b cutaneous melanoma, and should be considered and discussed with patients diagnosed with pT1b cutaneous melanoma for the purpose of staging, prognostication and determining eligibility for adjuvant therapy. Previously, the clinicopathologic and gene expression profile (CP-GEP, Merlin Assay®) model was developed to identify patients who can forgo SLNB because of a low risk for sentinel node metastasis. The aim of this study was to evaluate the clinical use and implementation of the CP-GEP model in a prospective multicenter study in the Netherlands. Both test performance and feasibility for clinical implementation were assessed in 260 patients with T1-T4 melanoma. The CP-GEP model demonstrated an overall negative predictive value of 96.7% and positive predictive value of 23.7%, with a potential SLNB reduction rate of 42.2% in patients with T1-T3 melanoma. With a median time of 16 days from initiation to return of test results, there was sufficient time left before the SLNB was performed. Based on these outcomes, the model may support clinical decision-making to identify patients who can forgo SLNB in clinical practice.

1. Introduction

Since the introduction of the sentinel lymph node biopsy (SLNB) technique in 1992 by Morton et al., it has become an essential step in melanoma staging [1,2]. Nowadays, international guidelines recommend SLNB for patients with cutaneous melanoma > pT1b [3–6]. Originally used for staging and prognostication, SLNB gained further significance with the introduction of adjuvant systemic therapy for high-risk stage III melanoma (including IIIA with nodal metastasis greater than 1 mm, IIIB and IIIC). As a result, the outcome of the SLNB currently determines eligibility for adjuvant therapy in clinical practice [7,8].

Approximately 75%–85% of patients who undergo SLNB have no nodal metastasis in the sentinel node (SN) [9–11]. Thus, in the majority of patients there are no therapeutic consequences (i.e. adjuvant systemic therapy) with the exception of patients with stage IIB/C melanoma, living in countries where adjuvant treatment for patients with high-risk stage II melanoma has been approved. Patients, undergoing SLNB, are however at risk, as 6–11% of patients experience postoperative complications such as wound infection and seroma [12,13]. In addition, the SLNB procedure requires multiple hospital visits with different specialists through in- and outpatient settings over multiple weeks [9]. After primary diagnosis, appropriate triage of patients who can safely forgo SLNB could decrease the number of surgeries and surgery-related

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complications, and limit the unnecessary burden for patients and healthcare resources.

Gene expression profiling (GEP) is one of the tools that has been shown to be able to identify patients with clinically apparent melanoma at low risk for SN metastasis [14–17]. It involves a genetic expression analysis of the primary melanoma at a transcription level, utilizing micro-arrays and real time PCR to molecularly profile the melanoma [14]. This information can be used to predict the development of metastasis or progression. Subsequently, it allows personalized treatment for patients with melanoma [18]. The Merlin Assay® is a clinically available test that uses the clinicopathological (CP)-GEP model, combining clinicopathological variables and gene expression of the primary melanoma to identify patients who have a low risk for SN metastasis [17]. While the model performance has widely been validated in independent cohorts in the US and Europe [14,19,20], and its clinical feasibility in US healthcare has been assessed, the use and applicability has not been evaluated in a prospective multicenter setting [21].

Therefore, the aim of this study was to evaluate clinical validation and implementation of the CP-GEP model in a multicenter prospective Dutch study.

2. Methods

2.1. Population

All eligible patients were included in four dedicated melanoma centers (Erasmus Medical Center (MC), Isala Hospital, Leiden University Medical Center and Maastricht University Medical Center) in the Netherlands from July 2020 until August 2022. Patients ≥18 years, with newly diagnosed primary cutaneous melanoma, eligible for SLNB (pT1b – pT4 according to American joint committee on cancer (AJCC) 8th edition) were assessed for study eligibility [6]. Exclusion was based on documented clinical positive nodes at diagnosis, satellite or in-transit metastases, or multiple primary melanomas with lymphatic drainage to the same lymph node basin. Other exclusion criteria included distant metastatic disease present at primary diagnosis, prior history of a primary invasive melanoma (>pT1b) within the last 5 years, non-cutaneous melanoma, and missing pathology report or paraffin embedded tissue of the primary melanoma.

The study was approved by the Erasmus MC Ethics Committee (MEC2020-0365) and local approval was provided by the participating centers. Signed informed consent for the use of the tissue of the primary melanoma was provided by all patients.

2.2. Sentinel lymph node biopsy and sentinel node mapping

The process of SN mapping and SLNB was consistently performed on the same day. During the morning of the SLNB, SN mapping was performed, exploring all nodal basins, using lymphoscintigraphy (4 × 15 MBq 99mTc-nanocolloid). If the affected SN was located in the parotic gland, the SLNB was omitted in consultation with the patient. After mapping, while the patient was being prepared for surgery, methylene blue was injected in the site of the primary melanoma. During the subsequent surgery the surgeon used a handheld gamma probe to detect the radioactive signal emitted by the SN. The use of methylene made the SN in question distinguishable from other lymph nodes. After identification, the SN was removed by the surgeon, and send to the pathologist for examination.

Histopathological analysis of the sentinel node (SN) was conducted according to the EORTC Melanoma Group pathology protocol [16].

2.3. CP-GEP model

The Merlin Assay® is a registered (CE-IVD), clinically available test that uses the CP-GEP model. The GEP includes the RNA expression of eight target genes associated with tumor development (i.e. *MLANA, GDF15, CXCL8, LOXL4, TGFBR1, ITGB3, PLAT and SERPINE2)* and two housekeeping genes. For the RNA expression to function optimally, it is necessary to collect the tissue that was first obtained. This is because a punch or shave biopsy results in wound healing and connective tissue forming. Consequently, if material collected at a later time is used, there could be potential overlapping with the molecular-level characteristics of the test signature. The ratios of the gene expression signals are subsequently combined with CP variables (age and Breslow thickness) in an algorithm to predict the outcome of the SLNB of an individual patient. Results of the CP-GEP model are expressed as a binary classification (low-risk or high-risk for nodal metastasis) [17]. In this study, all patients were planned for SLNB and the decision for surgery was not influenced by the results of the CP-GEP model.

2.4. Statistical analyses

Since all patients within a timeframe were included, no sample size calculation was performed. Clinical utility of the CP-GEP model was assessed in terms of organizational utility and predictive utility. Detailed descriptions of both outcomes are provided below. Statistical analyses were performed with SPSS version 28.0 (IBM, Armonk, NY, USA), with a P-value <0,05 (two-sided) indicating statistical significance.

2.5. Organizational utility

Organizational utility was assessed by measuring the overall time duration in the entire process, from informed consent (IC) to receipt of the test results, expressed in days. To gain a comprehensive understanding of the logistical aspects of the process, the overall time was subdivided into smaller intervals. The initial interval, referred to as the IC-to-revision interval, measured the time between the request for central revision and the central revision. In each participating center, upon obtaining of signed informed consent of the patient, a tissue revision request was submitted to the Department of Pathology of the coordinating center (Erasmus MC). The central revision encompassed a thorough examination of the hematotoxylin and eosin stained tissue and formalin-fixed paraffin-embedded (FFPE) tissue of the primary melanoma by an experienced melanoma pathologist at the Erasmus MC. If the diagnosis of melanoma was deemed incorrect after central revision, the patient was excluded from the study, no further steps for analyses were taken and findings of the revisions were shared with the referring physician. The revision-to-shipment interval denoted the duration from central revision completion to the shipment of tissue sample to the diagnostic lab of SkylineDx, located in Rotterdam, the Netherlands. Notably, central revision was leading for the diagnosis (e.g., if central revision deemed the initial diagnosis of melanoma incorrect or incomplete, the tissue was not shipped to the diagnostic lab for testing). In case of satellitosis, or incorrect diagnosis, the local investigator was notified. Following the revision, the samples were coded, and the accompanying pathology reports, including patient's age at time of excision and Breslow thickness, were anonymized before shipment to the diagnostic lab. The subsequent shipment-to-report interval represented the timespan between the shipment of tissue to the diagnostic lab and the receipt of the risk report for the CP-GEP. Within this interval, particular attention was given to the turnaround time, as defined by the number of workdays required by the diagnostic lab to complete the analysis. The CP-GEP score was determined and upon completion, risk reports were returned to the study coordinator in the Erasmus MC, who subsequently communicated risk outcomes to the treating physician. Lastly, *the IC-to-report* interval encompassed the entire sequence of activities, starting from the initiation of central revision request and concluding with the receipt of the risk report. A graphical representation of the intervals is presented in Fig. 1a and b.

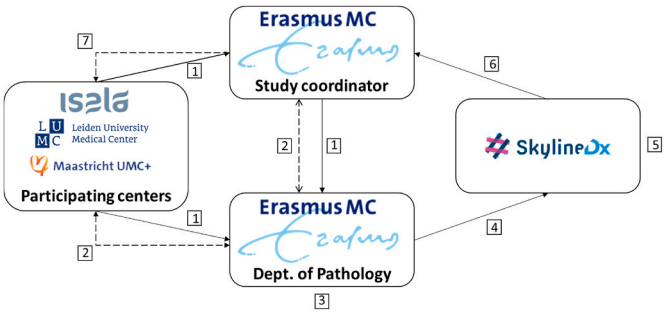

Fig. 1a. Visualization of process behind logistic utility.

Order-to-revision	Revision-to-shipment	Shipment-to-report
Order-to-report		

Fig. 1b. Visualization of intervals, 1. Participating centers send the test request-form to the Department of Pathology (DoP) and study coordinator at Erasmus MC. For patients included in the Erasmus MC, the study coordinator also forwards the request forms to the DoP 2. The DoP request Formalin-Fixed Paraffin-Embedded (FFPE) + hematoxylin and eosin (HE) stained tissue from participating centers and participating centers consequently sends requested FFPE + HE tissue (the combination of step 1 & 2 form the order-to-revision interval).3. The DoP revises and processes the FFPE + HE tissue. During this step, the tissue is anonymized. (Revision-to-shipment interval). 4. Shipping of processed and anonymized tissue to SkylineDx. 5. Conducting of Merlin Assay ® at SkylineDx. 6. SkylineDx transferring coded reports to study coordinator Erasmus MC. 7. Study coordinator informs participating centers on outcome risk report (the combination of step 4–6 form the shipment-to-report interval).

2.6. Predictive utility

Using the result of the SLNB pathology as the gold standard, the performance of the model was calculated. Model performance was assessed by calculating sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), SLNB reduction rate and corresponding 95% confidence intervals. SLNB reduction rate was calculated using the following formula [true negative + false negative]/[true negative + false negative + true positive + false positive]) and represented the percentage of patients that can forgo surgery based on the test outcome (i.e. CP-GEP low risk) [22]. The SLNB reduction rate was only calculated for patients who underwent SLNB. Subgroup analysis were performed according to T-stage based on the eighth version of the AJCC manual.

3. Results

3.1. Study population

Between July 2020 and November 2022, 279 patients with primary cutaneous melanoma were included across four participating centers. Nineteen patients (6.9%) were excluded after initial inclusion due to missing data or other reasons as depicted in Fig. 2. The median age was 63 years (IQR 50–71 years). The majority (n = 112, 43.1%) of patients had a T2 melanoma. An overview of baseline characteristics is provided in Table 1. Among the patients who did not undergo SLNB (n = 38, 14%), the reasons included patients' personal preference (n = 18), which was not based on CP-GEP outcome, localization of the SN in the parotid gland (n = 11), and the absence of a SN in pre-operative imaging (n = 9). A distribution of CP-GEP risk in patients who did not undergo a SLNB can be found in Table S1.

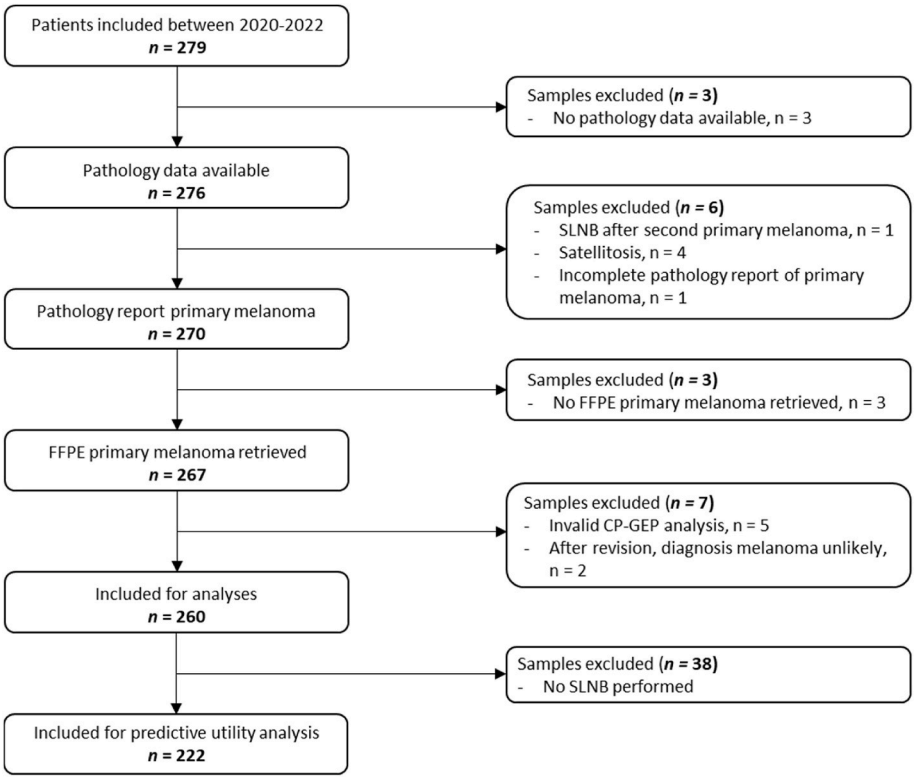

Fig. 2. Flowchart selection procedure. SLNB, sentinel lymph node biopsy; FFPE, formalin-fixed paraffin-embedded; CP-GEP, clinicopathological gene-expression profile.

Table 1
Baseline characteristics; n (%) or median (interquartile range).

	All patients n = 260	SLNB negative, n = 187	SLNB positive, n = 35	CP-GEP low risk, n = 100	CP-GEP high risk, n = 160
Sex, male	147 (56.5)	105 (56.1)	20 (57.1)	54 (54.0)	93 (58.1)
Age, years	63 (50–71)	62 (50–71)	60 (48–67)	63 (50–71)	63 (50–71)
Breslow thickness, mm	1.4 (1.0–2.2)	1.3 (1.0–1.9)	1.9 (1.2–3.0)	1.0 (0.8–1.1)	1.9 (1.3–3.0)
Ulceration					
Present	38 (14.6)	22 (11.8)	10 (28.6)	3 (3.0)	35 (21.9)
Absent	216 (83.1)	161 (86.1)	24 (68.6)	96 (96.0)	120 (75.0)
Unknown	6 (2.3)	4 (2.1)	1 (2.8)	1 (1.0)	5 (3.1)
T-stage, AJCC 8th edition					
T1					
T1b	74 (28.1)	59 (31.6)	3 (8.6)	61 (61.0)	13 (8.1)
T2	112 (41.5)	85 (45.5)	15 (42.9)	37 (37.0)	75 (46.9)
T2a	98 (37.7)	74 (39.6)	13 (37.1)	35 (35.0)	63 (39.4)
T2b	10 (3.8)	9 (4.8)	1 (2.9)	2 (2.0)	8 (5.0)
Ulceration status unknown	4 (1.5)	2 (1.1)	1 (2.9)	0	4 (2.5)
T3	54 (20.7)	33 (17.6)	11 (31.4)	2 (2.0)	52 (32.5)
T3a	38 (14.6)	25 (13.4)	7 (20.0)	1 (1.0)	36 (22.5)
T3b	15 (5.8)	7 (3.7)	4 (11.4)	1 (1.0)	14 (8.8)
Ulceration status unknown	1 (0.4)	1 (0.5)	0	0	2 (1.25)
T4	20 (7.7)	10 (5.3)	6 (17.1)	0	20 (12.5)
T4a	7 (2.7)	4 (2.1)	1 (2.9)	0	8 (5.0)
T4b	13 (5.0)	6 (3.2)	5 (14.3)	0	12 (7.5)
Tumor location					
Head/neck	60 (23.1)	33 (17.6)	5 (14.3)	20 (20.0)	40 (25.0)
Arm	51 (19.6)	38 (20.3)	9 (25.7)	21 (21.0)	30 (18.8)
Trunk	89 (34.2)	66 (35.3)	15 (42.9)	33 (33.0)	56 (35.1)
Leg	56 (21.5)	47 (25.1)	6 (17.1)	25 (25.0)	31 (19.4)
Missing	4 (1.6)	3 (1.7)	0	1 (1.0)	3 (1.9)

3.2. Organizational utility

The median IC-to-report time was 16 days (IQR 14–20 days). Results varied between healthcare facilities because of inconsistent IC-to-revision time, ranging between 4 and 11 days. In contrast, the revision-to-shipment interval and shipment-to-report interval were more consistent, with a median duration of four (IQR 2–6) and seven (IQR 6–9) days, respectively. Importantly, the median time required for the analyses at the diagnostic lab was 4 working days (IQR 4–5). Further information regarding logistic implementation is presented in Table 2.

An unexpected prolonged IC-to-report time was found in 16 patients, with a median value exceeding 30 days. The factors contributing to this increased interval included incorrect tissue shipment ($n = 4$) and an extended shipment duration (exceeding 25 days). In the first 30 patients, the IC-to-report interval was slightly longer, with a median of 18 days (IQR 13–23), compared to the overall patient population. This deviation was attributed to a logistic learning curve.

Table 2
Overview of organizational utility Expressed in Turn-around time in days, median (interquartile range).

	Overall n = 260	Hospital 1 n = 116	Hospital 2 n = 78	Hospital 3 n = 34	Hospital 4 n = 32
Order-to-revision	5 (3–6)	4 (2–5)	5 (3–6)	11 (7–11)	6.0 (5–7)
Revision-to-shipment	4 (2–6)	3 (1–6)	4 (2–6)	3 (2–6)	4.0 (2–5)
Shipment-to-report	7 (6–9)	7 (6–8)	8 (6–8)	7 (6–9)	9.0 (8–9)
Processing time at SkylineDx	4 (3–5)	–	–	–	–
Order-to-report	16 (14–20)	14 (13–18)	15 (13–20)	21 (17–30)	19 (16–20)

The interval 'Processing time at SkylineDx' is part of the 'Shipment-to-report' interval.

3.3. Predictive utility

SLNB was performed in 222 (85.4%) patients and SN metastases were detected in 35 (15.7%) of these 222 patients. The majority of these patients presented themselves with a T2 ($n = 15/222$) or T3 ($n = 11/222$) melanoma. Of the patients that did not undergo SLNB ($n = 38$), 25 patients had a CP-GEP report with high risk, and 13 patients had CP-GEP low risk (Table S2). One-hundred of 260 patients (38.5%) had a low risk for a positive SN. Among all patients, the model yielded a sensitivity of 91.4% (95% CI: 76.9–98.2), a specificity of 45.8% (95% CI: 38.6–53.2), a NPV of 96.7% (95% CI: 90.6–99.3) and a PPV of 23.7% (95% CI: 16.8–31.8). The SLNB reduction rate was 39.2% (95% CI: 32.7–45.9). For the group of patients with T1-T2 ($n = 186$, 71.5%) melanoma, in which the majority of CP-GEP low risk cases where found, the model yielded a sensitivity of 84.2% (95% CI: 60.4–96.6), a specificity of 57.3% (95% CI: 48.8–65.6), a NPV of 96.5% (95% CI: 90.0–99.2) and PPV of 20.7% (95% CI: 12.4–31.5). In this group, a SLNB reduction rate of 52.5% (95% CI: 44.5–60.5) was found. More specific information regarding model performance is shown in Table 3 and S2. In three cases, the CP-GEP model classified patients as low risk while the post-operative histopathological examination revealed nodal metastasis. Two of these patients had a micro-metastasis in the SN (max tumor diameter <0.1 mm).

4. Discussion

In this prospective multicenter study, the clinical validation and implementation of the CP-GEP model was assessed in patients with T1-T4 melanoma. In addition to earlier validation studies, this study investigated both the predictive utility and organizational utility.

Previously, Mulder et al. [14]and Yousaf et al. [20] reported NPV and sensitivity values for patients with T1-T3 melanoma that are similar to our study results. Mulder et al. reported an overall NPV of 90.5% (95% CI: 77.9–96.2) and a sensitivity of 91.5% (95% CI: 80.1–96.6), while Yousaf et al. reported a NPV of 93.8% (95% CI: 85–98.3) and a sensitivity of 90.0% (95% CI: 76.3–97.2)[14,20]. In the population described in this study, we observed similar results with a NPV of 96.5% (95% CI: 90.3–99.3) and sensitivity of 90.00 (95% CI: 73.5–97.9). In comparison to the validation studies of Mulder et al. [14] and Yousaf et al. [20], the number of patients with a CP-GEP low risk is remarkably higher in the current cohort; 20% and 31.2% vs. 38.5%, respectively. The difference in patient characteristics of the population could explain this variation, as the median Breslow thickness differed among the studies. Specifically, Mulder et al. reported a median thickness of 2.05 mm (IQR 1.40–3.30) and Yousaf et al. reported a median thickness of 1.8 mm (IQR 1.3–3.2), while the median thickness was 1.4 mm (IQR 1.0–2.2) in the current study. This difference in Breslow thickness also translated into a lower SN positivity rate in the current study.

While some minor variability due to small sample sizes may exist in our study, the performance in patients with pT2 melanoma is promising. Retrospective studies with CP-GEP reported NPVs ranging from 89.3% to 100%. In this prospective cohort we found an NPV of 100% suggesting that the amount of missed positive SN's when opting to omit surgery may be reduced. For instance, based on the current cohort and literature, patients with a pT2 melanoma have a 15% baseline risk for SN metastasis [23,24]. Employing the CP-GEP with a mean NPV of 95% would lead to a mere 5% of patients with a low-risk profile incorrectly opting to forgo surgery, in contrast to the 15% risk if all patients chose to omit surgery without utilizing the test. This implies that patients with pT2

Table 3
Predictive utility of Merlin Assay for the individual T-stages.

	T1-T4 (n = 222)	T1 (n = 62)	T2 (n = 100)	T3 (n = 44)	T4 (n = 16)
Sensitivity (95% CI)	91.4% (76.9–98.2)	0% (0–70.8)	100% (78.2–100.0)	100% (71.5–100)	100% (54.2–100.0)
Specificity (95% CI)	45.8% (38.6–53.2)	83.1% (71.0–91.6)	38.8% (28.4–50.0)	6.06% (0.74–20.2)	0% (0.0–30.9)
PPV (95% CI)	23.7% (16.8–31.8)	0% (0–30.9)	22.4% (13.1–34.2)	26.2% (13.9–42.0)	37.5% (15.2–64.6)
NPV (95% CI)	96.7% (90.6–99.3)	94.2% (84.1–98.8)	100% (89.4–100)	100% (15.8–100)	N.A.
SLNB RR (95% CI)	39.2% (32.7–45.9)	83.9% (72.3–92.0)	33.0% (23.9–43.1)	4.5% (0.6–15.5)	0 (0–20.6)

List of abbreviations: PPV; positive predictive value, NPV; negative predictive value, SLNB RR; sentinel lymph node biopsy reduction rate, CI; confidence interval.

melanoma and a low-risk CP-GEP may reasonably consider omitting the SLNB. With a SLNB reduction rate of 33% in patients with pT2, one in three patients will have a low-risk CP-GEP, indicating significant clinical benefits for this group. However, as the T-stage increases, the SLNB reduction rate decreases, suggesting that for thicker melanomas such as T3 and T4 extensive testing is required to identify patients with a low risk CP-GEP.

The clinical value of CP-GEP to reduce SLNB in patients with pT1b melanoma, needs to be discussed. In the study population, patients with pT1b melanoma had a low risk for SN metastasis (4.1%), indicating that the use of CP-GEP to identify patients with a low risk for nodal metastasis may not provide sufficient clinical utility. Although these results are based on small patient cohorts, future larger prospective studies including the MERLIN_001 trial will provide more comprehensive insights and help us establish a clearer understanding of the effectiveness of CP-GEP in guiding treatment decisions for patients with melanoma [25]. While the primary objective of a prediction model should be its prognostic accuracy, the duration it takes to complete the test is equally important for implementation in daily clinical practice. The logistics behind the test and the reporting of the results are required within acceptable timeframes, prior to the potentially scheduled SLNB. In 2016, Oude Ophuis et al. have shown that there is no effect of time interval between diagnosis and SLNB on 5-year survival or SN-positivity rate up to three months after diagnosis of primary melanoma [26]. Currently in the Netherlands, SLNB is consistently performed within this designated timeframe, unless unforeseen circumstances cause a delay. With a median time of 16 days between commencement of test and receipt of the results, the time frame is sufficient to discuss the test results with patients and consider to prevent surgery in patients with low-risk of SN positivity according to CP-GEP.

One potential limitation of this study is that it was conducted in four dedicated melanoma centers, which may lead to a relatively homogeneous study population. However, it is important to note that the population included in this study is likely to exhibit similarities with the broader population eligible for SLNB. This similarity can be attributed to the composition of the participating centers, which encompass both academic and teaching hospitals, with some academic institutions also serving as regional hospitals. As a result, the characteristics and diversity of the study population are expected to be representative and comparable to the general population eligible for SLNB.

If the model is incorporated into clinical practice, it has the potential to significantly reduce SLNBs, as the reduction rate is robust and significant when performed in the appropriate patient population (i.e. pT2) [19,20]. Consequently, although not actively investigated in this study, the incorporation of the CP-GEP model can be beneficial to patients for different reasons. First, after shared decision making, patients with a low-risk can forgo SLNB, decreasing the risk of complications associated with the SLNB, such as lymphedema and infection [12]. Second, the reduction in surgeries may result in a decrease in healthcare costs, and allow healthcare resources to be allocated to other departments, so that capacity issues may be addressed.

Despite the absence of mandatory consequences related to the surgical decision-making process in this particular study, we noted an increasing level of interest among both patients and physicians regarding the test results during the study, particularly in situations where patients with T1b melanoma were indecisive about undergoing surgery.

5. Conclusion

The CP-GEP model has a good organizational and predictive utility in a prospective multicenter study. The model may significantly improve the selection of patients, especially with T1b and T2a melanoma, who can forgo SLNB, reducing the risk of complications to which patients are exposed.

CRediT authorship contribution statement

Robert C. Stassen: Resources, Data curation, Formal analysis, Writing – original draft. **Evalyn E.A.P. Mulder:** Conceptualization, Methodology, Resources, Data curation, Writing – review & editing. **Antien L. Mooyaart:** Resources, Data curation, Writing – review & editing. **Anne Brecht Francken:** Resources, Writing – review & editing. **Jos van der Hage:** Resources, Writing – review & editing. **Maureen J.B. Aarts:** Resources, Writing – review & editing. **Astrid A.M. van der Veldt:** Writing – review & editing. **Cornelis Verhoef:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision. **Dirk J. Grünhagen:** Conceptualization, Methodology, Formal analysis, Resources, Writing – review & editing, Supervision.

Declaration of competing interest

This study was partially funded by SkylineDx. All other authors declare that they have no potential or competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2023.107249.

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