Predictive Performance of the Clinicopathologic Gene Expression Profile (CP-GEP) in Identifying Cutaneous Melanoma Patients for Whom Sentinel Lymph Node Biopsy is Unnecessary: A Systematic Review and Meta-Analysis Terence Wong¹, Sydney Ch'ng^{1,2,3}, Peter Ferguson^{1,2,3,4}, Linda Martin^{1,2}, Alexander M Menzies^{1,2,6,7}, Anne Cust^{1,5}, Inês Pires da Silva^{1,2,8,9}, Georgina V Long^{1,2,6,7}, Richard A Scolyer^{1,2,3,9}, Alexander van Akkooi^{1,2,3*}, Serigne N Lo^{1,2,9*}

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Background

- Sentinel lymph node biopsy (SLNB) is an invasive procedure used for accurate staging and optimal management^{1,2}
- SLNB is recommended for melanomas with Breslow thickness >1.0 mm and should be discussed for patients with thin melanomas²
- Overall rate of positive SLNBs is low, ranging from 15% to 20%³
- CP-GEP model serves as a deselection tool by identifying patients that do not have nodal metastasis and can therefore forgo SLNB

Objectives

Clinical Clinical Age Pathologic Breslow Thickness Pathologic Gene Expression Profiling GEP High risk SLNB recommended Low risk Safely forgo SLNB

Methods



External validation studies assessing the CP-GEP model from 2020-2024

To summarise the findings of multiple external validation studies across various countries to assess the overall predictive performance of the CP-GEP model and examine potential heterogeneity between validation cohorts



- True positive (TP), false positive (FP), true negative (TN), false negative (FN) values were extracted from each study to measure the predictive utility of the model (sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and SLNB reduction rate (RR)
- Pooled estimates were derived using a random-effects (RE) model
- Risk of bias: Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool
- SLNB reduction rate represents the proportion of patients that received a low-risk CP-GEP result and could therefore safely forgo SLNB⁴

SLNB reduction rate = $\frac{CP - GEP \ Low \ risk \ (TN + FN)}{AB}$

 $= \frac{1}{All \ patients \ (TN + TP + FP + FN)}$

- The overall pooled sensitivity was 93% and NPV was 95% across all primary tumour classification groups
- Subgroup analysis revealed that the model performed best for pT2 melanomas
- Results for pT1 melanomas could not be reliably interpreted as substantial heterogeneity was observed
- pT3 and pT4 melanomas are unlikely to benefit from the model as they have high risk for nodal metastasis and would usually be recommended to undergo SLNB

Studies from databases/registers (n = 33) Embase (n = 20) MEDLINE (n = 13)

Results

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Sensitivity	TP	FN		Proportion [95% CI]	Sensitivity	ТР	FN	Prop
Mulder 2020	52	4		⊷⊷ 0.93 [0.83, 0.98]	Mulder 2020	14	3	بــــــــــــــــــــــــــــــــــــ
Johansson 2021	51	3		⊷∎ 0.94 [0.85, 0.99]	Johansson 2021	17	2	⊧ ∎ i (
Yousaf 2021	40	4		⊷⊷ 0.91 [0.78, 0.97]	Yousaf 2021	16	1	⊢ ∎ -; (
Stassen 2023	32	3		└── - 0.91 [0.77, 0.98]	Stassen 2023	16	0	•
RE Model				◆ 0.93 [0.88, 0.96]	RE Model			
Specificity	TN	FP			Specificity	TN	FP	
Mulder 2020	38	116	⊢ ∎_j	0.25 [0.18, 0.32]	Mulder 2020	25	52	⊢ ∎ i
Johansson 2021	83	284	r an i	0.23 [0.18, 0.27]	Johansson 2021	67	124	⊢∎ → (
Yousaf 2021	61	103	 -4	0.37 [0.30, 0.45]	Yousaf 2021	18	44	⊢ - (
Stassen 2023	84	103	⊢ ∎1	0.45 [0.38, 0.52]	Stassen 2023	33	51	⊢ ∎(
RE Model				0.32 [0.23, 0.41]	RE Model			•
NPV	TN	FN			NPV	TN	FN	
Mulder 2020	38	4		└── - 0.90 [0.77, 0.97]	Mulder 2020	25	3	⊢ , (
Johansson 2021	83	3		⊢∎ 0.97 [0.90, 0.99]	Johansson 2021	67	2	⊢ ∎ (
Yousaf 2021	61	4		⊷⊷ 0.94 [0.85, 0.98]	Yousaf 2021	18	1	بــــــــــــــــــــــــــــــــــــ
Stassen 2023	84	3		⊢∎ 0.97 [0.90, 0.99]	Stassen 2023	33	0	⊢ ∎ 1
RE Model				 0.95 [0.92, 0.97] 	RE Model			- (
PPV	ТР	FP			PPV	ТР	FP	
Mulder 2020	52	116		0.31 [0.24, 0.39]	Mulder 2020	14	52	, <u> </u>
Johansson 2021	51	284	■ -1	0.15 [0.12, 0.20]	Johansson 2021	17	124	⊢ ∎⊣(
Yousaf 2021	40	103	⊢ =1	0.28 [0.21, 0.36]	Yousaf 2021	16	44	· · · · · (
Stassen 2023	32	103	 1	0.24 [0.17, 0.32]	Stassen 2023	16	51	⊢ ∎(
RE Model			-	0.24 [0.18, 0.31]	RE Model			- (
	CP-GE	P result				CP-GE	P result	t
SLNB RR	Low	High	:		SLNB RR	Low	High	i
Mulder 2020	42	168	⊢∎⊸	0.20 [0.15, 0.26]	Mulder 2020	28	66	⊢ ∎→ (
Johansson 2021	86	335		0.20 [0.17, 0.25]	Johansson 2021	69	141	⊢ ∎-⊣ (
Yousaf 2021	65	143	1 −−1	0.31 [0.25, 0.38]	Yousaf 2021	19	60	⊢ -

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Identificatio	References removed (n = 10) Duplicates identified manually (n = 2) Duplicates identified by Covidence (n = 8)									
	Studies screened (n = 23)									
ing										
Screen	Studies assessed for eligibility (n = 13) Studies excluded (n = 9) Abstract only (n = 1) Ongoing study (n = 1)									
	Wrong outcomes (n = 2) Wrong predictors (n = 5)									

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	Studios included in review (n - 1)
	Studies included in review (II = 4)
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C	

Figure 1. PRIMSA flowchart of search results and inclusion of external validation studies assessing the predictive utility of the CP-GEP model.



Figure 2. Pooled predictive performance metrics of the CP-GEP model for (A) all tumour thicknesses and (B) pT2 melanomas subgroup.

Conclusions

The CP-GEP model demonstrated the hallmarks of an effective deselection tool for SLNB, particularly in patients with pT2 melanomas
 Additional research into pT1 melanomas with greater sample sizes will be crucial in determining the true predictive utility of the model for this subgroup

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