Stromal gene expression predicts sentinel lymph node metastasis of primary cutaneous melanoma

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Background

- Cutaneous melanoma accounts for less than 5% of skin cancer cases but 75% of skin cancer deaths because of its ability to metastasize.[1,2]
- Staging of melanoma by AJCC 8th edition guidelines – the current classification system for describing the extent of disease and prognosis – relies on Breslow depth, ulceration, and whether disease has metastasized to sentinel lymph nodes (SLN) or beyond.[2,3,4]
- AJCC provides recommendations for patient selection for SLN biopsy (**Fig. 1**).
- More than 80% of patients who undergo SLN biopsy have no nodal metastasis and are unnecessarily exposed to procedure-induced morbidity such as lymphedema, seroma and infection.[5,6]

Objective

Develop expression-based molecular markers to identify patients for whom the risk of nodal metastasis is so low that they can safely forego SLN biopsy, thus reducing procedure-associated morbidity and prioritizing care for high risk patients.

Methods

- A targeted panel of gene expression assays was identified based on the analysis of RNA-Seq data, genomic databases, the cancer literature and case-control studies. 109 candidate biomarkers were selected and their expression was quantified in formalin-fixed paraffin-embedded diagnostic biopsy tissue across a cohort of 754 patients. All patients underwent SLN biopsy at Mayo Clinic within 90 days of diagnosis between 2004 and 2018. Clinicopathologic variables were abstracted from the electronic medical record. Histopathology was reviewed by two or more board-certified Mayo Clinic dermatopathologists.
- We used a penalized maximum likelihood estimation algorithm[8] to train logistic regression models in a repeated cross-validation scheme.[7] Models were generated based on only clinicopathologic variables (CLPA), only gene expression profiling (GEP), or a combination of clinicopathologic and gene expression variables (CLPA-GEP).

Results

- The combined model (CLPA-GEP) actionably changes the pre-test probability of SLN positivity for each T group (**Fig. 1**).
- The combined model (CLPA-GEP) can discriminate SLN+ from SLN- patients better than the models based solely on clinicopathologic variables or GEP (**Fig. 2**).
- The combined model (CLPA-GEP) can be used to reduce SLN biopsies while maintaining a high negative predictive value (**Fig. 3**).

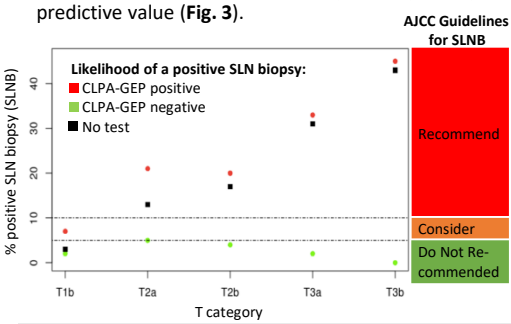

Fig. 1. *Risk of SLNB positivity by T categories.* For all T stages the likelihood of having a positive SLN is ≤5% for patients with a negative CLPA-GEP test. Hence they can safely forgo a SLN biopsy (see "do not recommend" area).

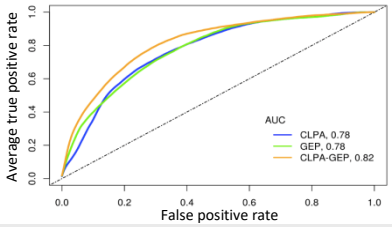

Fig. 2. *Average ROC curves and area under the ROC curve (AUC).* The CLPA-GEP has the highest AUC.

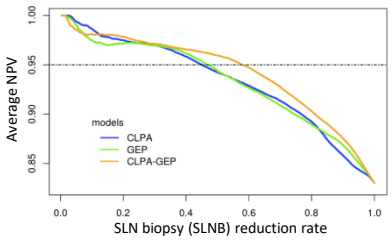

Fig. 3. *Average NPV vs. SLNB reduction rate.* The CLPA-GEP model achieves a SLN biopsy reduction rate of up to ~60% while keeping the false omission rate below 5%. NPV, negative predictive value.

Conclusions

The CLPA-GEP model based on age, Breslow depth and stromal gene expression outperforms all other models in:

- Identifying patients with a low risk (≤ 5%) of nodal metastasis who can safely forego a SLN biopsy **across all T categories**.
- Reducing SLN biopsy rates by up to ~60% while keeping the incorrect omission rate below 5%.

References and Disclosures

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