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Polygenic risk scores for melanoma: a stepwise process towards clinical implementation

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Linked Article: Steinberg et al. *Br J Dermatol* 2022; **186**:823–834.

Early detection of melanoma or, even better, preventing melanoma by educating and stimulating sun-protective behaviour, are still essential steps to reducing its global burden. However, evidence is insufficient to demonstrate the benefit of population-based screening by total body skin examination.¹ Potentially, focusing the screening on high-risk individuals may be cost effective. Clinical implementation of polygenic risk scores (PRSs) is increasingly mentioned to facilitate this identification of high-risk individuals (i.e. genetic risk stratification).

Although nowadays multiple PRSs for melanoma exist, external validation of the predictive performance of a PRS in an independent population is often absent. However, reproducibility is mentioned as an important issue in last year's published PRS Reporting Standards (PRS-RS).² Therefore, the paper by Steinberg et al.,³ in this issue, is an important study that evaluates three melanoma PRSs in addition to basic clinical characteristics derived from meta-analysis in two independent large cohorts.

The predictive performance of a model can be tested by the discriminant accuracy or area under the receiver operating characteristic curve (AUCROC). This determines if people who get a melanoma have a higher risk prediction than those who do not. Steinberg et al. showed that in both the UK Biobank (UKB) and Melbourne Collaborative Cohort Study (MCCS) discriminant ability increased from 0.03 to 0.10 by adding a PRS to age and sex, i.e. an integrated risk model.³ However, the overall AUCROC was still moderate at 0.69, suggesting that for population-based screening, the tested integrated risk models are not useful. The inclusion of single-nucleotide polymorphisms beyond those that meet stringent genome-wide association study significance levels or adding traditional melanoma risk factors may be considered to boost future predictive performance.

Most PRS studies present relative risks of melanoma. However, the authors of this study calculated the PRS-based sex- and age-specific 10-year absolute risk of melanoma.

Absolute risk scores provide more interpretable results and can even motivate behavioural changes. Using these absolute risk scores, the authors were also able to test the model's calibration, which compares the agreement between the expected and observed number of melanoma cases. Overall, they found that the model underpredicted incidence of melanoma, that is, fewer melanomas, compared with expected incidence. This would lead to falsely excluding high-risk patients. By adding the PRS to the risk model, estimations were closer to the observed number of cases in the UKB, but not in the MCCS sample. Different local healthcare systems and risk exposures per population are important reasons for misleading model outcomes.⁴ These findings emphasize the need to calibrate model performance in different settings.

In this study, Steinberg et al. show that implementation of PRSs in practice is still a considerable challenge, but they point us in the right direction.

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Janus kinase inhibitors for hidradenitis suppurativa: expanding the therapeutic toolbox

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In this issue of the *BJD*, Alavi et al. report two multicentre phase II trials designed to evaluate the safety and tolerability of the Janus kinase (JAK)1 inhibitor INCB054707 in patients with moderate-to-severe hidradenitis suppurativa (HS).¹ Treatment of patients with HS can be challenging, with variable and