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An independent external validation of melanoma risk prediction models using the Australian Melanoma Family Study

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None reported.

Dear Editor,
Risk prediction models, which include a combination of risk factors, have been developed as a more accurate way of estimating risk and personalising preventive interventions. Many melanoma risk prediction models have been published but few have been independently validated.[1] We aimed to externally validate 12 melanoma risk prediction models using the Australian Melanoma Family Study (AMFS), a population-based, case-control-family study comprising 629 incident first-primary melanoma cases, 240 population-based controls ascertained using the electoral roll (voting is compulsory) and 295 spouse or friend controls.[2] Recruitment took place from 2001 to 2005 in the states of New South Wales, Queensland and Victoria.

We focused on the clinical setting and excluded models with genetic predictors, as they are currently not being widely used. Model predictors were harmonised as close as possible to the AMFS variables (Supplementary S1-12; available from the corresponding author on request). In the AMFS, we calculated: (1) relative risk estimates for the model predictors; (2) discrimination, how well the model distinguishes between individuals of the same age with and without melanoma, using the area under the curve (AUC) and its 95% confidence interval using 1000 bootstrap procedures; and (3) overall calibration, agreement between the model's predicted and observed risk, using the Hosmer-Lemeshow test. We based the AUCs on relative risk, except for the Fears and Mar models where the authors reported 5 year absolute risk.[1] AMFS participants who had missing values for any of the predictors were excluded from the analysis (0.5 - 41.2 % participants excluded).

The 12 selected models were published between 1989 to 2015.[1,3,4] Fears, Mackie, and Sneyd published separate models for women and men.[1,3] The number of predictor variables in the models ranged from four to seven; the most common were the presence of naevi, freckle density, sunburn history and hair colour. The AMFS had equivalent or near equivalent variables for all the model variables, except for suspicious melanocytic lesion on dermoscopy in the Guther model. This variable was not measured in the AMFS and we used dysplastic naevi, it was clinically-accessed and established as having at least three of the following: ill-defined border, diameter more than 5mm, variegated colour, uneven outline and erythema, as a proxy.

Relative risk estimates for the model predictors were similar to the published relative risk estimates for that variable in each study (results not shown), except for suspicious melanocytic lesion on dermoscopy as expected. Discriminative performance on external validation ranged from 0.58 (95%CI 0.53-0.62) for the Cho model to 0.78 (95%CI 0.70-0.85) for the Fears model for men. The Mar model [AUC= 0.74 (95%CI 0.71-0.77)] and the Fears model for men [AUC= 0.78 (95%CI 0.70-0.85)] gave the highest discriminative performance in the Australian study. The melanoma risk prediction models from Davies et al, Sneyd et al, and Fortes et al also performed well in the AMFS. Discrimination was lower on external validation than for internal validation (Table). Sensitivity analyses found that reweighting the age and sex distributions of the AMFS controls minimally changed the AUCs (S13 and S14-25) The Hosmer-Lemeshow test p-value ranged from <0.0001 for both the Guther and Mackie model to 0.33 for the Fears model for men.

The discriminative performance of these 12 models is generally high and comparable to other melanoma and cancer risk prediction models, where AUCs range from 0.73 to 0.93 for melanoma,[5] 0.56 to 0.89 for breast cancer,[6] 0.63 to 0.70 for colorectal cancer[7] and 0.61 to 0.81 for lung cancer;[8] some of these models included age as a predictor. Similar to external validation studies of other cancer types, there is lower discrimination on external validation than on internal validation.[7,8] This could be due to model overfitting on internal validation, or to differences in participants' characteristics or study design.

Strengths of our study include the multi-centre, population-based design with histo-pathologically confirmed melanoma cases and comprehensive assessment of melanoma risk factors.

It is a limitation that we did not assess model calibration, which is more appropriately assessed using a cohort study. While we attempted to harmonise the predictor variables from other studies as closely as possible to variables in the AMFS, it is possible that there are differences in some variables that we treated as comparable. Other potential limitations include selection bias and recall bias associated with case-control studies.

In this external validation study of 12 melanoma prediction models, the largest number of melanoma models to be validated using a single independent dataset, we found several (Fears (men), Mar, Davies, Sneyd and Fortes) had sufficient discriminatory ability to stratify melanoma risk level and personalise prevention in clinical practice. However, most models had poor calibration, suggesting that they were not able to accurately predict number of cases in this study population.

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Supporting information is available from the corresponding author on request

Table S1-12. The model, its predictors, the comparable variable in the AMFS dataset, the relative risk estimates and participants included in the external validation analyses

S13. Procedure for reweighting the age and sex distribution of the AMFS controls to the general population

Table S14-25. AUC weights in the AMFS

Table. Model's discriminative performance as reported and on external validation (area under the receiver operating curve [AUC] and 95% confidence interval) using the Australian Melanoma Family Study

Published risk prediction model (Country)	Reported AUC (95% CI)	Unweighted-AUC (95% CI) on external validation	Weighted-AUC (95% CI) on external validation	Hosmer-Lemeshow test p-value
Cho et al, 2005 (United States)	0.62 (0.58-0.65) on internal validation	0.58 (95%CI 0.53-0.62)	0.58 (95%CI 0.54-0.62)	<.0001
Davies et al, 2015 (United Kingdom)	0.75 (0.73-0.78) on external validation	0.71 (95%CI 0.67-0.75)	0.72 (95%CI 0.68-0.76)	0.001
Fears et al, 2006 (United States)- model for women	0.70 for women ≥ 50 years	0.61 (95%CI 0.54-0.68)	0.60 (95%CI 0.52-0.68)	0.0003
Fears et al, 2006 (United States)- model for men	0.80 for men 20-49 years	0.78 (95%CI 0.70-0.85)	0.75 (95%CI 0.65-0.85)	0.33
Fortes et al, 2010 (Italy)	0.79 (0.75-0.82) on internal validation and 0.79 (0.70-0.86) on external validation	0.70 (95%CI 0.66-0.74)	0.68 (95%CI 0.64-0.73)	0.006
Guther et al, 2011 (United States)	0.86	0.64 (95%CI 0.60-0.67)	0.67 (95%CI 0.63-0.72)	<.0001
Mackie et al, 1986 (Scotland)- model for women	Not stated	0.64 (95%CI 0.58-0.70)	0.64 (95%CI 0.58-0.71)	0.0002
Mackie et al, 1986 (Scotland)- model for men	Not stated	0.66 (95%CI 0.59-0.74)	0.64 (95%CI 0.55-0.73)	<.0001
Mar et al, 2011 (Australia)	Not stated	0.74 (95%CI 0.71-0.77)	0.73 (95%CI 0.69-0.77)	0.0007

Sneyd et al, 2014 (New Zealand)- model for women	0.74	0.71 (95%CI 0.65-0.77)	0.71 (95%CI 0.64-0.79)	0.05
Sneyd et al, 2014 (New Zealand)- model for men	0.71	0.63 (95%CI 0.57-0.70)	0.66 (95%CI 0.57-0.74)	0.06
Williams et al, 2011 (United States)	0.70 (0.64-0.77)	0.67 (95%CI 0.64-0.70)	0.67 (95%CI 0.63-0.70)	0.03

CI, confidence interval