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ORIGINAL ARTICLE

FRAMe: Familial Risk Assessment of Melanoma—a risk prediction tool to guide *CDKN2A* germline mutation testing in Australian familial melanoma

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Abstract

Germline mutations in *CDKN2A* greatly increase risk of developing cutaneous melanoma. We have constructed a risk prediction model, Familial Risk Assessment of Melanoma (FRAMe), for estimating the likelihood of carrying a heritable *CDKN2A* mutation among Australian families, where the prevalence of these mutations is low. Using logistic regression, we analysed characteristics of 299 Australian families recruited through the Sydney site of GenoMEL (international melanoma genetics consortium) with at least three cases of cutaneous melanoma (in situ and invasive) among first-degree blood relatives, for predictors of the presence of a pathogenic *CDKN2A* mutation. The final multivariable prediction model was externally validated in an independent cohort of 61 melanoma kindreds recruited through GenoMEL Queensland. Family variables independently associated with the presence of a *CDKN2A* mutation in a multivariable model were number of individuals diagnosed with melanoma under 40 years of age, number of individuals diagnosed with more than one primary melanoma, and number of individuals blood related to a melanoma case in the first degree diagnosed with any cancer excluding melanoma and non-melanoma skin cancer. The number of individuals diagnosed with pancreatic cancer was not independently associated with mutation status. The risk prediction model had an area under the receiver operating characteristic curve (AUC) of 0.851 (95% CI 0.793, 0.909) in the training dataset, and 0.745 (95%CI 0.612, 0.877) in the validation dataset. This model is the first to be developed and validated using only Australian data, which is important given the higher rate of melanoma in the population. This model will help to effectively identify families suitable for genetic counselling and testing in areas of high ambient ultraviolet radiation. A user-friendly electronic nomogram is available at www.melanomarisk.org.au.

Keywords *CDKN2A* · Familial melanoma · Germline mutation · Genetic testing · Nomogram · GenoMEL

Introduction

Australia has the world's highest incidence of cutaneous melanoma, where it is one of the most common cancers diagnosed in the 15–40 years age bracket [1]. To date,

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CDKN2A remains the most commonly altered gene in familial melanoma, accounting for 20–40% of the inherited highly penetrant mutations found across several genes internationally (*CDKN2A*, *CDK4, TERT, TERF2IP, BAP1, ACD* and *POT1* [2–5]). However, the prevalence of these high-penetrance mutations is relatively low in Australian melanoma and this has been a barrier to systematic uptake of predictive testing, even for *CDKN2A*. Approximately 2.3% of Australian early-onset cases unselected for family history carry *CDKN2A* mutations [6] and even in the context of a strong family history, it accounts for no more than 20% of families [4, 7]. Lifetime risks to carriers are estimated to be 20% by age 50 years and 52% by age 80 years in population-based studies [8], but higher in multiple-case families (32% by age 50 years and 91% by age 80 years in Australia [9]).

Similarly to other common cancers, efforts have been made to create sensitive and specific screening programs to allow earlier detection and prevention in high-risk groups. A prospective Australian study of risk-stratified clinical surveillance for melanoma was found to be cost-effective [10–12]. Imparting genetic testing information to family members in high risk groups has shown the potential to instil behavioural change towards prevention [13] even in unaffected family members [14] and enhances understanding of risk and acceptance of recommendations compared to family history alone [15], including among younger age groups [16]. A model to quantitatively stratify families based on risk of carrying a *CDKN2A* mutation would be a valuable tool for clinical geneticists so that those with higher risk are channelled into appropriate counselling and testing whilst those with lower risk avoid unnecessary, expensive and invasive screening. In Australia it would overcome a key barrier to predictive testing by making it efficient enough to be deployed. Models predicting the presence of *CDKN2A* mutations have been published with datasets from American and Canadian families [17], the GEM Study (Australian, Canadian, American and Italian) families [18], Dutch and Swedish families [19], and more recently, the international GenoMEL Consortium (Australian, northern and southern American, northern and southern European and Middle Eastern) families [20]. The first three of these perform well with the given datasets but are limited by sample size and some possible bias due to founder mutations. The GenoMELPREDICT model is based on a much larger analysis, 2116 cases from 900 families across 29 study centres, including Australia (305 families from Sydney and 21 from Queensland) [20]. It expanded the original MELPredict model [17] by incorporating a history of pancreatic cancer and family phenotypes. Australian data comprised approximately 36% of the total cohort used in the GenoMELPREDICT model [20]. Some of the non-Australian families had 2 melanoma cases only and self-reports of pancreatic cancer were also included. Sensitivity analyses of the GenoMELPREDICT model indicated higher accuracy of the model after excluding the Australian dataset, suggesting that this cohort may differ to countries with a lower incidence of cutaneous melanoma.

EviQ is an Australian government online resource for evidence-based cancer treatment protocols hosted by the Cancer Institute of NSW [21]. The current EviQ consensus statement regarding the scope of genetic testing protocols for *CDKN2A* identifies the target population as "A person with familial cutaneous melanoma, defined as a member of a cluster of 3 or more confirmed cases in first and second degree blood relatives, with ≥ 20% pre-test probability of a pathogenic *CDKN2A* variant using the four factor GenoMELPREDICT score" or "where a known pathogenic variant is identified in a relative" [22].

To enhance the appropriateness and relevance of genetic testing for melanoma in Australian clinical services, we developed a risk prediction model specifically from Australian data that estimates the likelihood of carrying a *CDKN2A* mutation. This model is based on familial rather than individual phenotypes.

Methods

Participants

Participants and their family members were recruited to the prospective GenoMEL cohort study via its Sydney and Queensland centres. Queensland families were selected from those ascertained as part of the Q-MEGA project [23] or were recruited following referral from specialist clinicians. Participants were followed up via telephone interview and questionnaire. Informed consent was obtained for all participants and consent for use of de-identified data for the purposes of research was confirmed in accordance with each respective research centre's protocols (Sydney: HREC/13/CIPHS/71, Queensland: HREC/14/QPAH/495). Confirmation of melanoma status, pancreatic cancer, ocular melanoma and other cancers was ascertained through pathology reports, confirmation by physician, Australian cancer registry data and death certificates for both datasets. Specific care was taken to ensure all cancer reports confirmed; no unconfirmed self-reports were included.

Family definition

Families were selected if they had 3 or more confirmed cases of melanoma in blood relatives (up to third degree) and had been screened for *CDKN2A* mutation by full sequencing of coding exons (method previously described [24]) in at least two affected individuals. Families were classified as mutation positive if a *CDKN2A* variant with high probability

of pathogenicity had been found [6, 25, 26]. Other cancers (excluding non-melanoma skin cancers) were included in the analysis if they occurred in first-degree relatives of a melanoma case. The Sydney site data comprised 299 families and the validating dataset provided by the Queensland site, comprised 61 families.

Data analysis

Potential predictors considered for inclusion in the risk prediction model were: number of individuals in a family with: confirmed cutaneous or ocular melanoma; a first primary melanoma diagnosed before the age of 40 years; multiple primaries; pancreatic cancer; other cancers excluding pancreatic and non-melanoma skin cancers. Family characteristics were summarised by their frequency. To build the model to predict the presence of a pathogenic *CDKN2A* mutation using the Sydney cohort (training dataset), we first ran a univariable logistic regression model considering all family characteristics. Variables with a p-value less than 0.20 were selected as potential predictors. Then, a multivariable analysis including all potential predictors was built and a backwards selection model applied to derive the final predictive model. Model performance was assessed through discrimination and calibration indices. Discrimination was evaluated using the area under the receiver-operating characteristic curve (AUC) and calibration of the model was assessed by comparison of the predicted and observed risks of presence of a pathogenic *CDKN2A* mutation. An AUC of 0.5 indicates no prediction ability and 1.0 means the model perfectly discriminates families with and without *CDKN2A* mutation [27]. The calibration of the model was assessed by comparing the predicted and observed risks of presence of *CDKN2A* mutation. Risk groups were defined according to deciles of risk score from the prediction model. Within each group, the average predicted risk was plotted against the proportion observed to have a *CDKN2A* mutation; linear regression was performed and the R^2 coefficient was taken as the quantitative calibration. The model's goodness-of-fit was also tested using the Hosmer–Lemeshow test. Next, we assessed the external validation of the risk prediction model, using the Queensland cohort (an independent validation dataset) to assess the performance (discrimination and calibration) of the model [28]. An online and hard-copy nomogram was created to facilitate clinical use; this is a graphical representation of the model that translates the identified risk factors into a scoring system that correlates to familial mutation risk.

Results

Training dataset

In the training (Sydney) dataset, a *CDKN2A* mutation was present in 40 (13.4%) families, with non-mutation families accounting for 259 (86.6%) of the 299 families. See Supplementary Table 1 for a summary of the cohort characteristics and Supplementary Table 2 for a list of the *CDKN2A* mutations observed. The variables considered in the analysis are listed in Table 1. See Supplementary Table 3 for a summary of the cancer types observed.

Table 2 displays the results of the univariable and multivariable regression analyses. All of the variables achieved significance (p-value < 0.05). Therefore, all of the variables were included in the multivariable analysis and a backward variables selection procedure performed. The final predictive model included three variables: number of individuals in a family diagnosed with melanoma under 40 years of age, number of individuals in a family with > 1 primary melanoma and number of individuals in a family with cancers other than melanoma (excluding non-melanoma skin cancer). Results of testing additional variables for univariable association are listed in Supplementary Table 4 and show that all variables counting cancers other than melanoma were associated with mutation status, regardless of whether pancreatic cancer was counted or not.

Figure 1 shows the AUC representing the discriminative ability of the model to accurately predict *CDKN2A* mutation status; the AUC was 0.851 (95% CI 0.793, 0.909), indicating a good ability to discriminate between families that carry versus don't carry a mutation.

The calibration plot indicated that the risk prediction model was well-calibrated, with a good linear correlation between predicted probabilities of the presence of a *CDKN2A* mutation and observed probabilities ($R^2 = 0.953$), see Fig. 2. Furthermore, the p-value for the Hosmer–Lemeshow test was 0.77, indicating good agreement between observed and predicted probabilities overall and within subgroups of participants.

External validation

The performance of the model was then externally assessed using the Queensland validation cohort. Figure 1b showed good discrimination ability with an AUC of 0.745 (95% CI 0.61–0.88). The calibration plot also showed good concordance between the predicted and the observed risk of the presence of a *CDKN2A* mutation, with an R^2 of 0.953 (Fig. 2). The nomogram is shown in Fig. 3.

Table 1 Summary of family characteristics

Family characteristic[a]	Number of families	
	Sydney development cohort (n = 299)	Queensland validation cohort (n = 61)
CDKN2A family mutation		
0	263 (88.0%)	39 (63.9%)
1	36 (12.0%)	22 (36.1%)
Number of people in the family with:		
Melanoma		
3	154 (51.5%)	14 (23.0%)
4	78 (26.1%)	8 (13.1%)
≥ 5	67 (22.4%)	39 (63.9%)
Melanoma at age < 40 year		
0	81 (27.1%)	9 (14.8%)
1	103 (34.4%)	19 (31.1%)
2	69 (23.1%)	11 (18.0%)
≥ 3	46 (15.4%)	22 (36.1%)
More than 1 primary melanoma		
0	102 (34.1%)	7 (11.5%)
≥ 1	197 (65.9%)	54 (88.5%)
Pancreatic cancer		
0	281 (94.0%)	53 (86.9%)
≥ 1	18 (6.0%)	8 (13.1%)
Any cancer other than melanoma or pancreatic cancer		
0–1	235 (78.6%)	13 (21.3%)
≥ 2	64 (21.4%)	48 (78.7%)
Any cancer other than melanoma		
0–1	230 (76.9%)	13 (21.3%)
≥ 2	69 (23.1%)	48 (78.7%)
Melanoma, but no other cancer		
1	5 (1.7%)	3 (4.9%)
2	39 (13.0%)	13 (21.3%)
3	131 (43.8%)	7 (11.5%)
4	68 (22.7%)	8 (13.1%)
5	30 (10.0%)	10 (16.4%)
6 to 14	26 (8.7%)	20 (32.8%)
Melanoma, and at least one other cancer		
0	207 (69.2%)	14 (23.0%)
1	77 (25.8%)	20 (32.8%)
2	12 (4.0%)	13 (21.3%)
3	2 (0.7%)	12 (19.7%)
4 to 7	1 (0.3%)	1 (3.3%)
Any cancer other than melanoma, but no melanoma		
0	197 (65.9%)	11 (18.0%)
1	67 (22.4%)	12 (19.7%)
2	22 (7.4%)	14 (23.0%)
3	10 (3.3%)	9 (14.8%)
4 to 9	3 (1.0%)	15 (24.6%)
Both melanoma and pancreatic cancer		
0	293 (98.0%)	59 (96.7%)
1 or 2	6 (2.0%)	2 (3.3%)

Table 1 (continued)

Family characteristic[a]	Number of families	
	Sydney development cohort (n = 299)	Queensland validation cohort (n = 61)
At least 1 cancer other than melanoma		
0	152 (50.8%)	3 (4.9%)
1	85 (28.4%)	14 (23.0%)
2	36 (12.0%)	10 (16.4%)
3	15 (5.0%)	12 (19.7%)
4 to 6	11 (3.7%)	22 (36.1%)
At least 2 cancers other than melanoma		
0	288 (96.3%)	35 (57.4%)
1	9 (3.0%)	22 (36.1%)
2 or 3	2 (0.7%)	4 (6.6%)
At least 3 cancers other than melanoma		
0	295 (98.7%)	56 (91.8%)
1 or 2	3 (1.3%)	5 (8.2%)

[a]Cancers other than melanoma were counted if confirmed in a melanoma case or a first-degree blood relative of a melanoma case; non-melanoma skin (keratinocyte) cancers (NMSC) were excluded

Table 2 Family characteristics predicting CDKN2A family mutation—univariable and multivariable regression analysis

Variable	Univariable		Multivariable[‡]	
Number of people in the family[a] with:	OR (95% CI)	P-value	OR (95% CI)	P-value
Melanoma				
3	1	0.0004		
4	1.54 (0.62, 3.84)			
≥ 5	4.68 (2.12, 10.36)			
Melanoma < age 40 years				
0	1	< .0001	1	< 0.0001
1	1.33 (0.31, 5.72)		1.31 (0.29, 5.78)	
2	4.93 (1.32, 18.48)		5.30 (1.36, 20.58)	
≥ 3	21.84 (6.01, 79.41)		18.22 (4.80, 69.08)	
More than 1 primary melanoma				
0	1	0.0017	1	0.0077
≥ 1	5.48 (1.89, 15.86)		4.70 (1.50, 14.40)	
Pancreatic cancer				
0	1	0.0220		
≥ 1	3.34 (1.19, 9.37)			
Any cancer other than melanoma or pancreatic cancer				
0–1	1	0.0001		
≥ 2	3.89 (1.93, 7.84)			
Any cancer other than melanoma				
0–1	1	< 0.0001	1	0.0012
≥ 2	4.29 (2.14, 8.57)		3.76 (1.68, 8.40)	

[‡]Final model obtained after using backward selection procedure, the model intercept was − 2.297

[a]Cancers other than melanoma were counted if confirmed in a melanoma case or a first-degree blood relative of a melanoma case; non-melanoma skin (keratinocyte) cancers (NMSC) were excluded

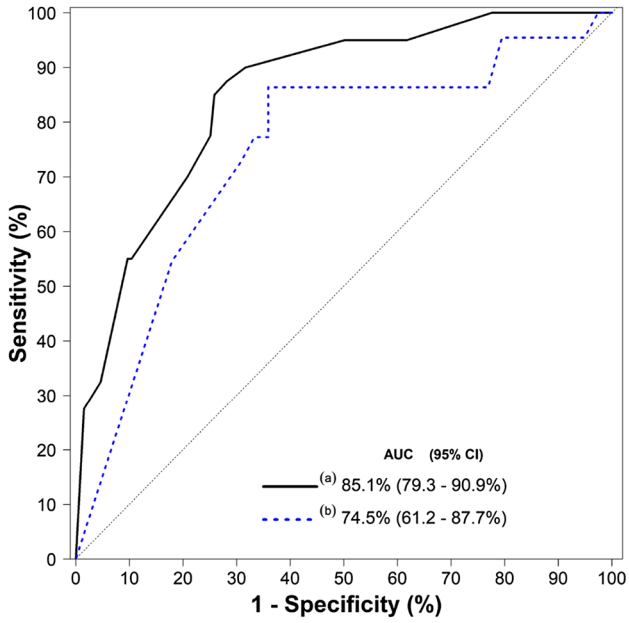

Fig. 1 **a** Receiver operating characteristic (ROC) curve using the Sydney (training) dataset (solid line) and **b** ROC curve using the Queensland (validation) dataset (dotted line)

An online version of this nomogram is publicly available at www.melanomarisk.org.au

Discussion

This model predicts the presence of *CDKN2A* mutations in Australian melanoma families with high accuracy and enables families to be efficiently selected for predictive testing. The most recent global model GenoMELPREDICT was comprised of 36% Australian families (305 families from the Sydney site) [20]. The GenoMELPREDICT three- and four-predictor models achieved AUCs of 0.748 (95%CI 0.726, 0.771) and 0.772 (95%CI 0.750, 0.793) when including the Australian Sydney subset and AUCs of 0.772 (95%CI 0.747, 0.797) and 0.784 (95%CI 0.760, 0.808) after excluding the Sydney data [20]. The AUC's for Australian participants overall was 0.809 (95% CI 0.773, 0.844) for both three and four variable GenoMELPREDICT models. Our Australian model achieved an AUC of 0.851 (95%CI 0.793, 0.909) in the development dataset and is therefore likely to be superior for application in Australian clinics. Another strength of our study is its external validation in an independent Australian dataset, which indicated lower but still high discrimination of 0.745 (95% CI 0.612 to 0.877).

Other cancers have been reported in melanoma prone families [29–33]. We included any other cancer confirmed in a first-degree relative of a person with melanoma in our analysis. The variety of cancer types confirmed across all the families was broad with the most commonly observed cancers correlating with the most commonly diagnosed cancers in the Australian population (breast, prostate and colorectal cancer) [1]. Cancers of the upper airway (larynx, pharynx or oral cavity) were a contributor to the CM-Score model which performs well in prediction of CDKN2A mutation for both Dutch and Swedish cohorts where the p16 Leiden deletion (Dutch) and p.Arg112dup (Swedish) mutations predominate [19]. A point of difference between these cohorts and the Australian cohort is the absence of a founder mutation effect and the presence of a very heterogeneous mix of *CDKN2A* variants.

A notable difference between the Australian model and GenoMELPREDICT is that the inclusion of pancreatic cancer did not significantly improve discrimination for the

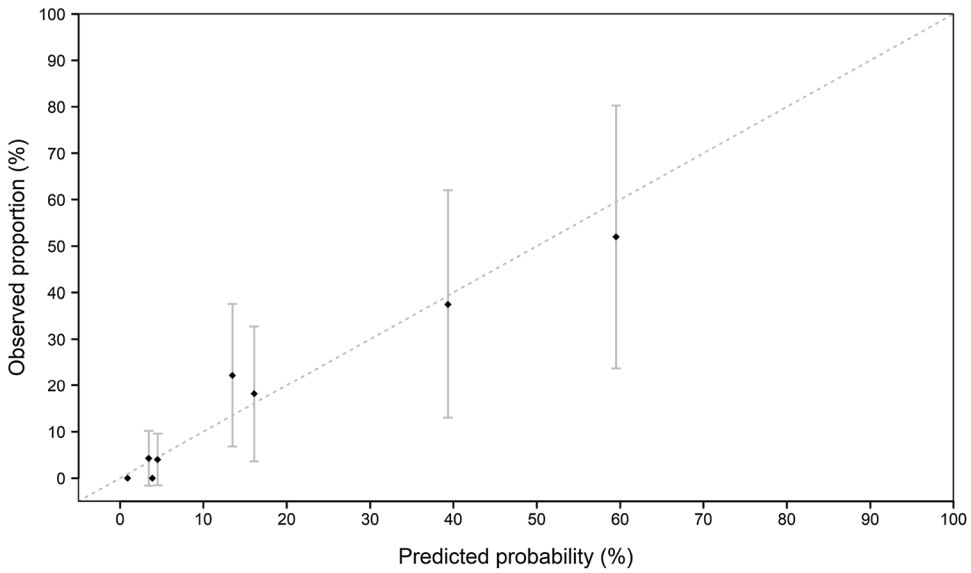

Fig. 2 Calibration plot comparing predicted versus observed numbers of positive-mutation families, in the external validation (Queensland) dataset

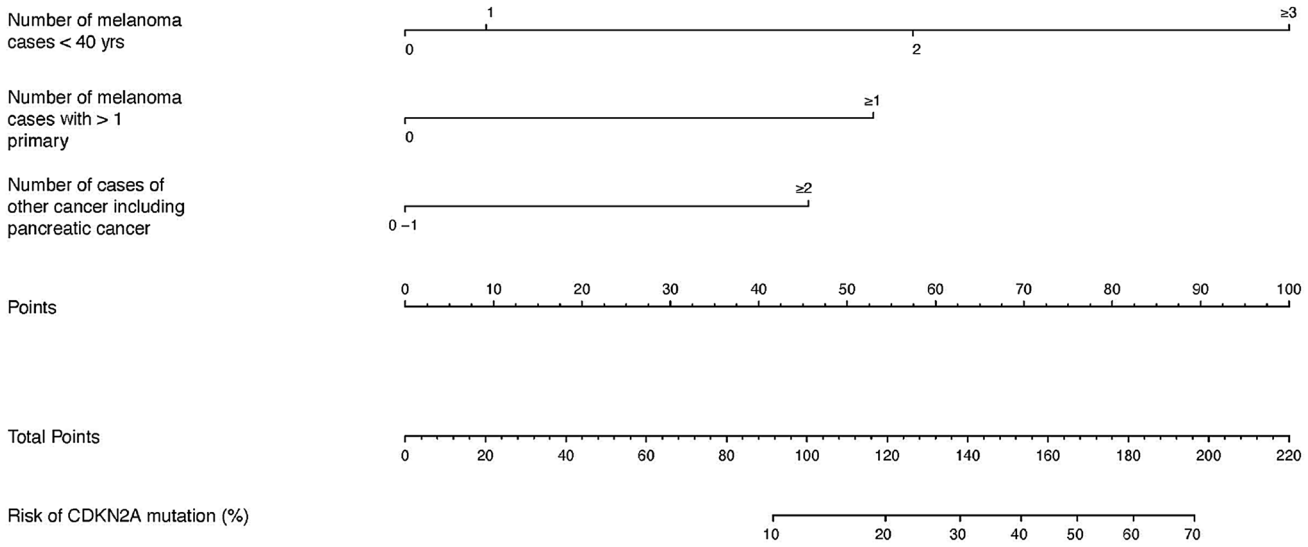

Fig. 3 Nomogram for estimating individual family risk of having a positive *CDKN2A* mutation. To use the nomogram, the values for each prediction parameter are marked. From each mark, a vertical line is drawn upwards to determine the "Points", and the points are added together. This total value is marked on the "Total Points" line, and a vertical line is followed downwards to the accompanying line labelled "Risk of positive *CDKN2A* mutation". The corresponding value on this line indicates the predicted risk the patient's family will carry a positive *CDKN2A* mutation. For instance, a family where two members have been diagnosed with melanoma before age 40 years, with no more than one primary at each diagnosis, and two other first degree family members each diagnosed with any cancer (other than melanoma and excluding NMSC) would have a total score of 106 points (58 + 0 + 48) which corresponds to an estimated risk of positive *CDKN2A* mutation of ~ 12%. An online version of this nomogram is publicly available at www.melanomarisk.org.au

Australian model. This is consistent with the low overall prevalence of pancreatic cancer in Australian *CDKN2A* mutation positive families, noted previously [30]. Our evidence is that a personal or family history of any other cancer should be taken into account when assessing a family's genetic risk. A count of internal malignancies other than melanoma but including pancreatic cancer was included in the final Australian model and confirms that the number of first degree relatives with other cancers in melanoma families is also a relevant predictor of a *CDKN2A* mutation [29, 33].

The Sydney dataset had a 13% prevalence of *CDKN2A* mutations, in contrast to the Queensland dataset which had a prevalence approximately 3 times higher (36% families were mutation positive). This may be explained by the greater number of larger families in the validation dataset (64% with 5 or more cases of melanoma) compared to the Sydney cohort (22%). Nevertheless, despite the different family sizes and mutation prevalence, the model still had very high discriminatory performance in predicting a *CDKN2A* mutation in the family.

It is estimated that carriers of *CDKN2A* germline mutations have more than a 31-fold greater risk of melanoma compared to the population (95% CI 20–50) [8]. In primary cutaneous melanomas, 5-year survival rates drop from approximately 99% for thin melanomas (≤ 1 mm; T1a-T1b) to 93–96% (stages T2a-T2b), 86–94% (stages T3a-T3b) and 82–90% (stages T4a-T4b) [34] and prognosis worsens with increasing age [35]. Early detection is therefore important for better survival outcomes. Identification of high-risk patients can lead to improved care, surveillance [12] and prevention behaviours [16, 36], and increase the likelihood of detecting new and recurrent melanomas at an earlier stage. Further, non-melanoma cancers are often observed [29] and have been reported to be overrepresented among melanoma affected *CDKN2A* carriers compared to affected noncarriers within families (41.3% diagnosed with other tumours in *CDKN2A* positive versus 27.0% in negative melanoma cases) [37]. Our model has shown that the number of individuals related in the first degree and diagnosed with other cancers in a melanoma family can be a predictor of a family *CDKN2A* mutation. This mobilises more information from the family history than a count of pancreatic cancers alone. Our model will contribute to more efficient identification of *CDKN2A* positive families and therefore *CDKN2A* mutation positive individuals in the community. They can be offered evidence-based interventions such as intensified primary prevention, education to recognise lesions and specialised surveillance including regular full skin checks by clinicians supported by total body photography and digital dermoscopy to improve prevention and early detection outcomes [38].

The risk model and the derived nomogram, based on familial rather than individual characteristics, are a useful addition to the current national guidelines for genetic testing

in melanoma in Australia, where the overall prevalence of these mutations is low [22, 39]. We recommend implementation of this risk prediction tool into clinical genetics and general melanoma practices in Australia and other countries with high ambient ultra violet radiation (UVR) with further prospective validation of the performance of the model.

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Compliance with ethical standards

Conflict of interest The authors have all declared that they have no conflict of interest.

Ethical approval Human Research Ethics Committees Sydney: HREC/13/CIPHS/71, Queensland: HREC/14/QPAH/495

References

1. Australian Institute of Health and Welfare, *Cancer in Australia 2019*. 2019: Canberra:AIHW.
2. Aoude LG et al (2015) Genetics of familial melanoma: 20 years after CDKN2A. Pigment Cell Melanoma Res 28(2):148–160
3. Potrony M et al (2015) Update in genetic susceptibility in melanoma. Ann Transl Med 3(15):210
4. Read J, Wadt KA, Hayward NK (2016) Melanoma genetics. J Med Genet 53(1):1–14
5. Law MH, Macgregor S, Hayward NK (2012) Melanoma genetics: recent findings take us beyond well-traveled pathways. J Invest Dermatol 132(7):1763–1774
6. Harland M et al (2014) Prevalence and predictors of germline CDKN2A mutations for melanoma cases from Australia, Spain and the United Kingdom. Hered Cancer Clin Pract 12(1):20
7. Goldstein AM et al (2007) Features associated with germline CDKN2A mutations: a GenoMEL study of melanoma-prone families from three continents. J Med Genet 44(2):99–106
8. Cust AE et al (2011) Melanoma risk for CDKN2A mutation carriers who are relatives of population-based case carriers in Australia and the UK. J Med Genet 48(4):266–272
9. Bishop DT et al (2002) Geographical variation in the penetrance of CDKN2A mutations for melanoma. J Natl Cancer Inst 94(12):894–903
10. Watts CG et al (2018) A national budget impact analysis of a specialised surveillance programme for individuals at very high risk of melanoma in Australia. Appl Health Econ Health Policy 16(2):235–242
11. Watts CG et al (2017) Cost-Effectiveness of skin surveillance through a specialized clinic for patients at high risk of melanoma. J Clin Oncol 35(1):63–71
12. Watts CG et al (2015) Clinical practice guidelines for identification, screening and follow-up of individuals at high risk of primary cutaneous melanoma: a systematic review. Br J Dermatol 172(1):33–47
13. Kasparian NA et al (2009) Genetic testing for melanoma risk: a prospective cohort study of uptake and outcomes among Australian families. Genet Med 11(4):265–278
14. Aspinwall LG et al (2014) Unaffected family members report improvements in daily routine sun protection 2 years following melanoma genetic testing. Genet Med 16(11):846–853
15. Taber JM et al (2015) Genetic test reporting enhances understanding of risk information and acceptance of prevention recommendations compared to family history-based counseling alone. J Behav Med 38(5):740–753
16. Morton RL et al (2019) Risk attitudes and sun protection behaviour: Can behaviour be altered by using a melanoma genomic risk intervention? Cancer Epidemiol 61:8–13
17. Niendorf KB et al (2006) MELPREDICT: a logistic regression model to estimate CDKN2A carrier probability. J Med Genet 43(6):501–506
18. Wang W et al (2010) Estimating CDKN2A carrier probability and personalizing cancer risk assessments in hereditary melanoma using MelaPRO. Cancer Res 70(2):552–559
19. Potjer TP et al (2018) CM-Score: a validated scoring system to predict CDKN2A germline mutations in melanoma families from Northern Europe. J Med Genet 55(10):661–668
20. Taylor NJ et al (2019) Estimating CDKN2A mutation carrier probability among global familial melanoma cases using GenoMELPREDICT. J Am Acad Dermatol 81(2):386–394
21. eviQ:https://www.eviq.org.au.
22. eviQ:https://www.eviq.org.au/cancer-genetics/adult/genetic-testing-for-heritable-pathogenic-variants/1864-cdkn2a-genetic-testing#, 2020.
23. Baxter AJ et al (2008) The Queensland Study of Melanoma: Environmental and Genetic Associations (Q-MEGA); study design, baseline characteristics, and repeatability of phenotype and sun exposure measures. Twin Res Hum Genet 11(2):183–196
24. Harland M et al (2008) A comparison of CDKN2A mutation detection within the melanoma genetics consortium (GenoMEL). Eur J Cancer 44(9):1269–1274
25. Taylor NJ et al (2016) Phenotypic and histopathological tumor characteristics according to CDKN2A mutation status among affected members of melanoma families. J Invest Dermatol 136(5):1066–1069
26. Miller PJ et al (2011) Classifying variants of CDKN2A using computational and laboratory studies. Hum Mutat 32(8):900–911
27. Wald NJ, Bestwick JP (2014) Is the area under an ROC curve a valid measure of the performance of a screening or diagnostic test? J Med Screen 21(1):51–56
28. Steyerberg EW et al (2010) Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology 21(1):128–138
29. Leachman SA et al (2017) Identification, genetic testing, and management of hereditary melanoma. Cancer Metastasis Rev 36(1):77–90
30. Goldstein AM et al (2006) High-risk melanoma susceptibility genes and pancreatic cancer, neural system tumors, and uveal melanoma across GenoMEL. Cancer Res 66(20):9818–9828
31. Soura E et al (2016) Hereditary melanoma: update on syndromes and management: emerging melanoma cancer complexes and genetic counseling. J Am Acad Dermatol 74(3):395–407

32. Jouenne F et al (2017) Germline CDKN2A/P16INK4A mutations contribute to genetic determinism of sarcoma. J Med Genet 54(9):607–612
33. Mukherjee B et al (2012) Risk of non-melanoma cancers in first-degree relatives of CDKN2A mutation carriers. J Natl Cancer Inst 104(12):953–956
34. Gershenwald JE et al (2017) Melanoma staging: evidence-based changes in the American joint committee on cancer eighth edition cancer staging manual. CA Cancer J Clin 67(6):472–492
35. Indicators, N.C.C., *National cancer control indicators: National cancer stage at diagnosis data*. 2018, Cancer Australia.
36. Aspinwall LG et al (2008) CDKN2A/p16 genetic test reporting improves early detection intentions and practices in high-risk melanoma families. Cancer Epidemiol Biomarkers Prev 17(6):1510–1519
37. Helgadottir H et al (2016) Germline CDKN2A mutation status and survival in familial melanoma cases. J Natl Cancer Inst 108(11):135
38. Mann, G., A/Prof Anne Cust, Damian, D, Paul Fishburn, Kelly, J, Victoria Mar MBBS, FACD, PhD, Soyer, P, Cancer council Australia melanoma guidelines working party. What interventions have been shown to reduce the risk of death from melanoma in those assessed to be at high risk of new primary melanoma? https://wiki.cancer.org.au/australiawiki/index.php?oldid=186156, Accessed Feb 28, 2020. Available from https://wiki.cancer.org.au/australia/Clinical_question:What_interventions_reduce_risk_of_death_from_melanoma_in_high_risk_people%3F. In: Cancer Council Australia Melanoma Guidelines Working Party. Clinical practice guidelines for the diagnosis and management of melanoma. Sydney: Cancer Council Australia. https://wiki.cancer.org.au/australia/Guidelines:Melanoma.
39. https://wiki.cancer.org.au/australiawiki/index.php?oldid=209426, Accessed Feb 28, 2020. Available from: https://wiki.cancer.org.au/australia/Guidelines:Melanoma..