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Clinical practice guidelines for identification, screening and follow-up of individuals at high risk of primary cutaneous melanoma: a systematic review*

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Summary

Understanding how individuals at high-risk of primary cutaneous melanoma are best identified, screened and followed up will help optimize melanoma prevention strategies and clinical management. We conducted a systematic review of international clinical practice guidelines and documented the quality of supporting evidence for recommendations for clinical management of individuals at high risk of melanoma. Guidelines published between January 2000 and July 2014 were identified from a systematic search of Medline, Embase and four guideline databases; 34 guidelines from 20 countries were included. High-risk characteristics that were consistently reported included many melanocytic naevi, dysplastic naevi, family history, large congenital naevi, and Fitzpatrick Type I and II skin types. Most guidelines identify risk factors and recommend that individuals at high risk of cutaneous melanoma be monitored, but only half of the guidelines provide recommendations for screening based on level of risk. There is disagreement in screening and follow-up recommendations for those with an increased risk of future melanoma. High-level evidence supports long-term screening of individuals at high risk and monitoring using dermoscopy. Evidence is low for defining screening intervals and duration of follow-up, and for skin self-examination, although education about skin self-examination is widely encouraged. Clinical practice guidelines would benefit from a dedicated section for identification, screening and follow-up of individuals at high risk of melanoma. Guidelines could be improved with clear definitions of multiple naevi, family history and frequency of follow-up. Research examining the benefits and costs of alternative management strategies for groups at high risk will enhance the quality of recommendations.

What's already known about this topic?

- The rationale for screening and follow-up of people at high risk of melanoma is that earlier diagnosis leads to decreased morbidity, medical costs and patient anxiety.

What does this study add?

- A summary of risk factors for 'high' and 'very high' risk groups.
- A summary of the levels of evidence for different clinical recommendations aimed at individuals at high risk.

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- A systematic review that demonstrates there is variation on definitions of high risk; and disagreement about recommendations for screening methods or follow-up based on the level of risk for a future cutaneous melanoma.

In most countries with populations of predominantly European origin, incidence rates of cutaneous melanoma have increased over the past decade.[1,2] The general rationale for screening and follow-up of people at high risk of melanoma is based on evidence that earlier diagnosis leads to decreased morbidity,[3] reduced medical costs[4] and decreased anxiety.[5] Population screening is currently not recommended in most countries.

Understanding how individuals at high risk of primary cutaneous melanoma are best identified, screened and followed up will help optimize melanoma prevention strategies and clinical management of melanoma. This includes uncertainty about which groups in the general population should be monitored more closely, and what the efficient optimal screening and follow-up intervals are from health outcomes and economic perspectives.[6–8] Unlike guidelines for primary treatment and staging of melanoma, which are relatively standardized,[9] recommendations for follow-up after a melanoma diagnosis appear to differ by country.[10]

The aim of this systematic review was to examine international clinical practice guidelines for identification, screening (prior to melanoma diagnosis) and follow-up (after melanoma diagnosis) of individuals at high risk of primary cutaneous melanoma, and the quality of the evidence supporting their recommendations. Our purpose was to identify areas of strength and weakness in this evidence base and therefore inform scientific and clinical discussion regarding the management of individuals at high risk of melanoma. We did not address recommendations for management of congenital naevi, follow-up for local, regional or distant recurrence, or recommendations relating to family members.

Methods

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[11] checklist.

Data sources

Two separate strategies were used to identify clinical practice guidelines published between January 2000 and July 2014. Firstly, we performed a literature search for guidelines using Medline ('melanoma.mp' AND 'practice guideline') and Embase ('melanoma'/exp AND 'practice guideline'/de). Second, we searched the following guideline databases using the search term 'melanoma':

1 International Guideline Library of the Guidelines International Network (GIN)
2 Turning Research Into Practice (Trip) Database
3 National Guideline Clearinghouse database based within the Agency for Healthcare Research and Quality (AHRQ)
4 Canadian Medical Association (CMA) Clinical Practice Guidelines Database.

Study selection

Titles and abstracts from Medline and Embase were screened and the full text of potentially relevant manuscripts was examined to identify relevant guidelines. The guideline databases mainly contained clinical recommendations and provided a reference to the country and organization responsible for the recommendations. In all cases, we attempted to source the original and most recently published guideline. We included guidelines that focused on prevention or risk factors for cutaneous melanoma, identification of individuals at high risk of melanoma, or included management of patient care in relation to melanoma screening or follow-up. When there was a range of guidelines from a single country, we selected national guidelines that had been created by government health organizations and nationally recognized professional groups (e.g. American Academy of Dermatology). If national guidelines were not available, we included regional guidelines created by a guidelines committee or group of referring centres, or guidelines produced by opinion leaders or referring centres that were targeted at healthcare professionals.

Based on the title and abstract, publications were excluded if:

1 the guidelines had a singular focus on pathology, oncology or surgical techniques related to melanoma diagnosis or treatment
2 the guidelines did not include recommendations for cutaneous melanoma
3 they were described by the authors as a review, overview or guide
4 guidelines were superseded by a later publication from the same authors or group
5 the intended audience was the general public or a specific specialist group (e.g. nurses).

When eligibility for inclusion in the review was unclear, the guidelines were discussed with co-authors A.E.C. and R.L.M. and selection agreed by consensus. If the guideline could not be sourced in English, Google Translate (www.translate.google.com.au) was used for translation.

Data extraction

From the clinical practice guidelines, we extracted information regarding the following:

1 Description of melanoma risk factors, particularly identification of high-risk groups. For follow-up, we selected risk factors for development of a subsequent primary melanoma.
2 Recommendations for screening prior to melanoma diagnosis, and follow-up after melanoma diagnosis for a subsequent primary melanoma and whether there was a specific recommendation for 'high-risk' groups.
3 The intended audience and quality of evidence supporting the recommendations.

We summarized and collated the key clinical recommendations in the guidelines.

Quality assessment of the evidence supporting the guideline recommendations

To standardize the levels of evidence stated in each guideline, we used the Oxford Centre for Evidence-Based Medicine validated appraisal tool[12] for which the evaluation of evidence was based around the question 'what interventions are recommended in the guidelines for people at greatest risk of melanoma?' (see Supplementary Table S1). This was considered to be the most relevant tool for the review. Levels of evidence were graded as 'high' if the strongest levels of evidence (i.e. level 1 or level 2) were provided, 'low' if the evidence was graded as level 3 or level 4, and 'very low' if the evidence was based on 'mechanistic reasoning' (level 5) including recommendations arising from expert opinion. Two reviewers (C.G.W. and M.D.) assessed the levels of evidence as stated in the original guideline. Where definitions of the levels of evidence in guidelines were similar to the Oxford definitions, levels were mapped across. Where levels were not provided (Table 1), the references cited for the recommendation were reviewed by C.G.W. and M.D. and a level of evidence was assigned using the Oxford table. When opinions differed on the level of evidence between reviewers, the guidelines were discussed and consensus reached.

Results

Literature search results

We initially identified 981 publications meeting our search criteria, and after excluding 947 ineligible publications, 34 guidelines from 20 countries were included in the review (Fig. 1). Most ineligible publications were reporting research results (e.g. related to melanoma therapies) that could have implications for guidelines, or were guidelines about specific treatments or procedures. Just over half of the guidelines (18 of 34) reviewed were produced since 2010.

Risk factor identification

Almost all (32 of 34) of the clinical practice guidelines stated that some groups in the population have an increased risk of melanoma; however, the number of risk factors identified in the guidelines varied considerably (from 0 to 17) (Table 1). These risk factors fell within four categories which could be broadly summarized as: naevi; other phenotypic features such as fair skin; ultraviolet (UV) exposure; and a miscellaneous group (e.g. history of previous melanoma, family history, rare genetic conditions and immunosuppression). There was a wide range of terminology used to describe risk factors from the general to the specific: for example multiple naevi were described as 'many moles', 'increased naevi' or '> 50 or 100 naevi'. While UV exposure was cited by most guidelines as a major risk factor, 12 guidelines[13–24] listed indoor tanning beds as a risk factor.

We examined melanoma risk factors by region and identified which risk factors were found in more than 50% of guidelines (Fig. 2). High naevus counts, dysplastic naevi, Fitzpatrick skin type I or II,[25] and family history predominated in all guidelines. European guidelines were different from those of North America and the Southern hemisphere as they include a history of intermittent sun exposure as a risk factor; the majority (75%) of guidelines from the Southern hemisphere countries included actinic or solar lentigines (measures of chronic sun exposure).

Definition of high-risk groups

While most guidelines mentioned risk factors, 25 (73%) recommended risk assessment for melanoma. Of these, 20 defined what was meant by risk assessment,[13,14,16,18,19,21,23,24,26–37] describing this within a context of the medical history and clinical assessment of the patient or selection for screening which could occur opportunistically or when a patient attends with a suspicious lesion. Supplementary Table S2 shows a summary of the different countries' guidelines regarding assessment of level of risk, applicable to high-risk individuals. An increase in risk due to possession of more than one risk factor was described in seven guidelines.[13,14,20,21,23,35,37]

Sixteen (47%) guidelines described an 'increased' or 'high' risk group compared with the general population. Nine guidelines[13,14,16,21,23,24,28,31,33] described three levels of risk: average, high and 'very high' or 'extreme' risk; these high-risk classifications are described in Table 2. Some guidelines provided summary relative risks for the different risk factors, from which we selected those conferring a relative risk > 4 as 'very high' risk; this cut-off point was chosen to be consistent with most guidelines that provided both relative risks and risk categories, whereby relative risks of 1–4 were generally classified as 'high' and relative risks above 4 as 'very high' risk. In general, risk factors that conferred the highest risk were: CDKN2A mutation carriers, > 100 naevi, > 5 atypical naevi, a

Table 1 Appraisal of guidelines by country summarizing target audience, evidence base for recommendations, screening and follow-up recommendations for high-risk individuals (n = 34 guidelines)

			Screening (prior to cutaneous melanoma)		Follow-up (for subsequent primary lesion)		
Country	Guideline	Target audience	Number of risk factors	Differentiation of levels of risk	Number of risk factors	Specific recommendation for high-risk people	Evidence base for creation of guideline
Australia/ New Zealand	ACNMGRWP (2008)[13]	Clinicians and healthcare professionals	13	Yes	3	Yes	Systematic literature review, critical appraisal, evidence-based summary and levels of evidence. Grading of recommendation
Austria/Italy	Zalaudek *et al.* (2005)[41]	Not stated	13	No	0	No	Evidence-based review by committee. No levels of evidence or grading of recommendations[b]
Brazil	Brazilian Society of Dermatology (2005)[46]	Not stated	0	No	3	Yes	Evidence-based review by committee. Levels of evidence for recommendation provided
Canada	Alberta Health Service (2011)[47]	Clinicians and health workers[a]	0	No	0	No	Systematic literature review and evidence-based summary. Summary of evidence level, no grading of recommendations[b]
	BC Cancer Agency (2013)[15]	Clinicians	11	No	0	No	Evidence-based review by committee. No level of evidence or grading of recommendation[b]
	Cancer Care Ontario Program (2007)[14]	Clinicians[a]	13	Yes	0	No	Systematic literature review, critical appraisal, evidence-based summary. Summary of evidence level, no grading of recommendations[b]
	Canadian Expert Panel on Malignant Melanoma (2009)[29]	Clinicians	9	No	0	No	Evidence-based review by committee. No level of evidence or grading of recommendations[b]
Europe[c]	EDF, EADO, EORTC (2012)[38]	Clinicians and healthcare specialists	7	No	1	No	Evidence-based review by committee. No level of evidence or grading of recommendations[b]
	ESMO (2012)[42]	Not stated	1	No	0	No	Evidence-based review by committee. Levels of evidence for recommendation provided and grading of recommendations
Finland	Finnish Medical Society (2012)[20]	Clinicians and healthcare providers	7	No	0	Yes	Systematic literature review and evidence-based summary. Levels of evidence for recommendation provided

Table 1 (continued)

Country	Guideline	Target audience	Screening (prior to cutaneous melanoma)		Follow-up (for subsequent primary lesion)		Evidence base for creation of guideline
			Number of risk factors	Differentiation of levels of risk	Number of risk factors	Specific recommendation for high-risk people	
France	French National Cancer Institute (2012)[26]	Clinicians	13	No	2	Yes	Evidence-based review by committee. No level of evidence or grading of recommendations[b]
	French Society of Dermatology (2007)[45]	All healthcare professionals	0	No	3	No	Systematic literature review, critical appraisal, evidence-based summary and levels of evidence. Grading of recommendation
Germany	German Dermatologic Society; Dermatologic Cooperative Oncology Group (2013)[37]	All healthcare professionals	11	Yes	2	Yes	Systematic literature review, critical appraisal, evidence-based summary and levels of evidence. Grading of recommendation and strength of consensus for recommendation
Italy	Italian Group of Dermatology and Oncology and Multidisciplinary Group on Melanoma (2007)[39]	Not stated	4	No	2	Yes	Evidence-based review by committee. Summary compiled following expert consensus conference. No level of evidence or grading of recommendation[b]
Netherlands	Dutch Working Group on Melanoma (2013)[21]	Clinicians and healthcare providers	11	Yes	0	No	Systematic literature review, critical appraisal, evidence-based summary and levels of evidence. Grading of recommendation
New Zealand	New Zealand Guidelines Group (2009)[44]	Primary care clinicians[a]	8	Yes	0	No	Systematic literature review, critical appraisal, evidence-based summary and levels of evidence. Grading of recommendation
Norway	Guidelines Working Group (2011)[19]	General practitioners and specialists	9	No	2	Yes	Systematic literature review, critical appraisal, evidence-based summary and levels of evidence. Grading of recommendation
Poland	Rutkowski *et al.* (2013)[18]	Not stated	6	No	0	No	Evidence-based review by committee. No level of evidence or grading of recommendations[b]
South Africa	Melanoma Advisory Board (2004)[27]	Physicians	8	No	0	No	Consensus recommendation based on review of evidence by committee. No level of evidence or grading of recommendations[b]

Table 1 (continued)

Country	Guideline	Target audience	Screening (prior to cutaneous melanoma)		Follow-up (for subsequent primary lesion)		Evidence base for creation of guideline
			Number of risk factors	Differentiation of levels of risk	Number of risk factors	Specific recommendation for high-risk people	
Spain	Mangas *et al.* (2010)[35]	Clinicians	13	No	2	Yes	Consensus recommendation based on review of evidence by committee. No level of evidence or grading of recommendations[b]
	Villalobos León *et al.* (2013)[22]	Not stated	14	No	0	No	Evidence-based review. No level of evidence or grading of recommendations[b]
Switzerland	Dummer *et al.* (2012)[42]	Clinicians	7	No	2	No	Consensus recommendation based on review of evidence by committee. Limited explanation of levels of evidence based on grading of recommendations
Ukraine	Guidelines Working Group (2014)[24]	Specialists and family doctors	6	Yes	0	No	Systematic literature review, critical appraisal and evidence-based summary and levels of evidence. Grading of recommendations
U.K.	British Association of Dermatologists Clinical Standards Unit (2010)[16]	Clinicians	14	Yes	1	Yes	Systematic literature review, critical appraisal and evidence-based summary and levels of evidence. Grading of recommendations
	Concise Guidelines (2007)[33]	Physicians, general practitioners and healthcare professionals[a]	7	Yes	0	No	Systematic literature review, critical appraisal and evidence-based summary and levels of evidence. Grading of recommendations
	National Institute for Health and Clinical Excellence (2006)[30]	Healthcare professionals in primary care[a]	7	No	0	No	Systematic literature review, critical appraisal and evidence-based summary and recommendation provided. Summary of evidence level, no grading of recommendations[b]
	Sowerby Centre for Health Informatics at Newcastle (2011)[31]	Healthcare professionals in primary care[a]	15	Yes	0	No	Systematic literature review, critical appraisal and evidence-based summary and recommendation provided. Summary of evidence level, no grading of recommendations[b]

Table 1 (continued)

Country	Guideline	Target audience	Screening (prior to cutaneous melanoma)		Follow-up (for subsequent primary lesion)		Evidence base for creation of guideline
			Number of risk factors	Differentiation of levels of risk	Number of risk factors	Specific recommendation for high-risk people	
	Royal College of Surgeons in Ireland (2006)[17]	Clinicians	11	No	1	Yes	Consensus recommendation based on review of evidence by committee. Levels of evidence for recommendation provided and grading of recommendations
	Scottish Intercollegiate Guidelines Network (2003)[28]	Healthcare professionals	17	Yes	0	No	Systematic literature review, critical appraisal and evidence-based summary and level of evidence. Grading of recommendations
U.S.A.	National Comprehensive Cancer Network (2014)[36]	Clinicians and healthcare providers	7	No	3	Yes	Systematic literature review, critical appraisal and evidence-based summary and levels of evidence. Grading of recommendations based on level of evidence and consensus[b]
	American Academy of Dermatology (2011)[40]	Not stated	0	No	3	Yes	Systematic literature review, critical appraisal and evidence-based summary and levels of evidence. Grading of recommendations
	National Cancer Institute (2014)[23]	Healthcare professionals	11	No	0	Yes	Systematic literature review, critical appraisal and evidence-based summary and levels of evidence. No grading of recommendations
	U.S. Preventive Services Task Force (2009)[34]	Clinicians[a]	6	No	0	Yes	Consensus recommendation based on review of evidence by committee. Summary of evidence level, no grading of recommendations[b]
	American Society of Plastic Surgeons (2007)[32]	Healthcare practitioners	5	No	3	Yes	Systematic literature review, critical appraisal and evidence-based summary and levels of evidence. Grading of recommendations

ACNMGRWP Australian Cancer Network Melanoma Guidelines Revision Working Party; EDF, European Dermatology Forum; EADO, European Association of Dermato-Oncology; EORTC, European Organization for Research and Treatment of Cancer; ESMO, European Society for Medical Oncology. [a]These guidelines focus mainly on initial assessment and referral (of particular interest to primary care physicians). [b]Levels of evidence for recommendations were not provided in the guidelines or could not be mapped. References provided in guidelines were assessed by reviewers (C.G.W. and M.D.) using the 2011 Oxford levels of evidence. [c]Greece is included in ESMO and counted as one of the 20 countries included in the review.

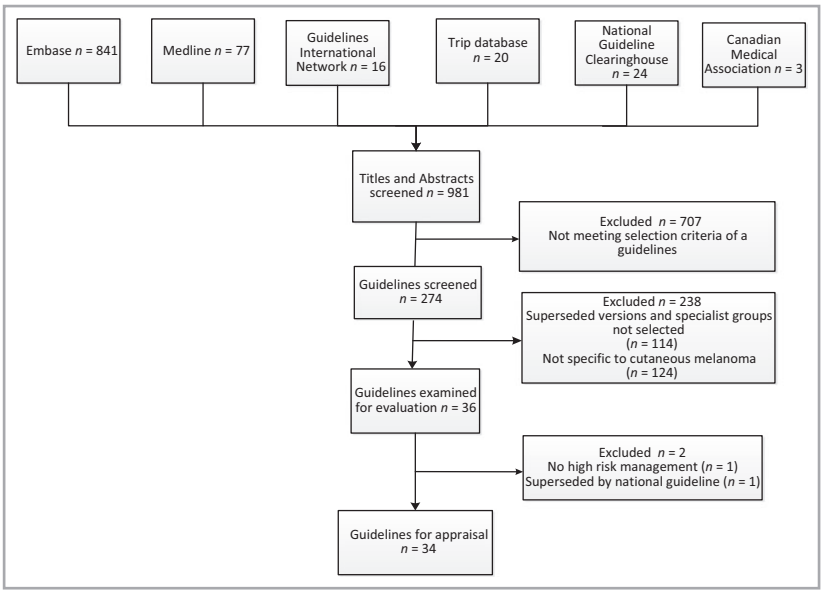

Fig 1. Flow chart for literature search.

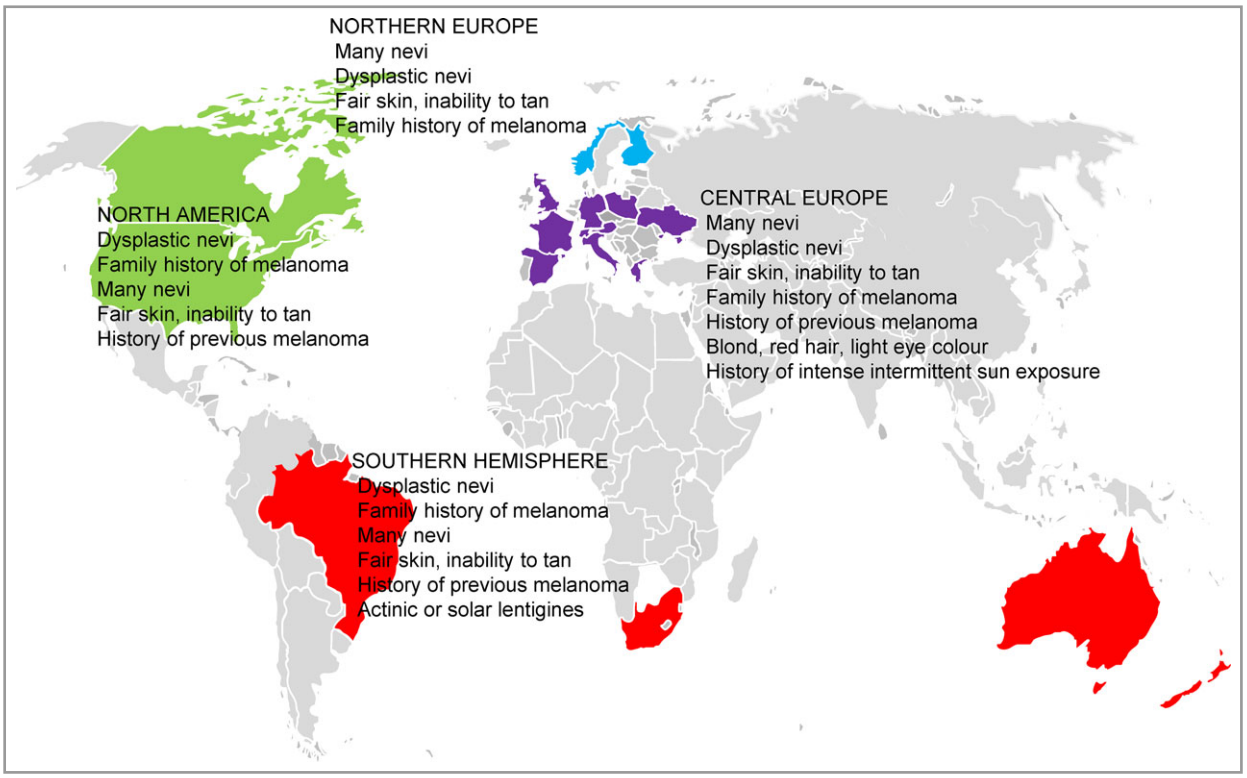

Fig 2. Geographical region as basis for categorization of risk factors. The most frequently mentioned melanoma risk factors in order, identified from at least half the guidelines from Northern Europe (blue), Central Europe (purple), and North America and Canada (green) and the Southern hemisphere countries (red). Countries without published clinical practice guidelines meeting the inclusion criteria for this systematic review (grey).

strong family history of melanoma (i.e. 2 to 31-degree relatives with confirmed melanoma) and a personal history of melanoma (Table 2).

While family history was mentioned in 25 guidelines (73%), there were different definitions for this term. Genetic predisposition, usually with regard to CDKN2A mutations, was listed in eight guidelines.[13,19,21–23,28–30]

Guideline recommendations for screening prior to melanoma diagnosis

Supplementary Table S3 shows a summary of the different countries' guidelines regarding screening management, applicable to high-risk individuals. Over half (58%) of the guidelines provided recommendations for screening based on

Table 2 Risk factors differentiated into 'high risk' and 'very high risk' groups in guidelines[a]

Country	Guideline	High risk	Very high risk
Australia and New Zealand	Australian Cancer Network Melanoma Guidelines Revision Working Party (2008)[13]	Increased number of naevi	> 100 naevi
		Clinically atypical naevi	> 5 atypical naevi
		Family history (melanoma in one 1st-degree relative)	CDKN2A mutation in a familial setting
		Fitzpatrick scale skin type I or II	
		History of nonmelanoma skin cancer	
Canada	Cancer Care Ontario Program (2007)[14]	Many (50–100) naevi	> 100 naevi
		One or more atypical (dysplastic) naevi	> 5 atypical naevi
		Family history (melanoma in one 1st-degree relative)	Two or more cases of melanoma in 1st-degree relatives
		Fitzpatrick scale skin type I or II	Personal history of skin cancer
		Freckles	Immunosuppressive therapy due to organ transplant
		Naturally red or blond hair	> 250 treatments with psoralen plus ultraviolet radiation (PUVA) for psoriasis
			History of radiation therapy in childhood
Netherlands	Dutch Working Group on Melanoma (2013)[21]	Fitzpatrick scale skin type I or II	Families with high-risk melanoma-associated gene mutations CDKN2A and familial atypical multiple mole melanoma syndrome
		Red hair colour	Three or more melanomas, of which two are in 1st-degree relatives or three melanomas of which two melanomas occur in one individual and the affected persons are 1st-degree relatives
		Freckling	Second-degree relatives of CDKN2A-positive families
		Actinic skin damage	> 100 naevi
		Blond hair colour	> 5 atypical naevi
			Large congenital naevus
			A medical history of previous skin cancer
Ukraine	Guidelines Working Group (2014)[24]	Multiple naevi	Family history of three or more affected family members or history of pancreatic cancer
		Organ transplant recipients	Family history of two or more affected family members with history of multiple primary melanoma or atypical mole phenotype
		History of melanoma	Congenital naevi > 20 cm
U.K.	British Association of Dermatologists Clinical Standards Unit (2010)[16]	Increased number of naevi	Atypical naevus syndrome
		Clinically atypical naevi	Giant congenital naevi > 20 mm or > 5% body surface area
		A family history (at least two cases of melanoma)	A strong family history (at least three cases of melanoma)
		Immunosuppressed due to organ transplant	A strong family history (three cases of melanoma or pancreatic cancer)
		History of a previous melanoma	History of multiple melanomas or pancreatic cancer
	Concise Guidelines (2007)[33]	Freckles	> 100 naevi
		Red hair or Fitzpatrick scale skin type I or II	Atypical naevi
		Family history (melanoma in one 1st-degree relative)	Two or more cases of melanoma in 1st-degree relatives

Table 2 (continued)

Country	Guideline	High risk	Very high risk
	Sowerby Centre for Health Informatics at Newcastle (2011)[31]	> 50 naevi	> 100 naevi
		Family history of skin cancer	A strong family history (at least three cases of melanoma)
		Immunosuppressed	Multiple atypical naevi
		Personal history of melanoma	Giant congenital naevi > 20 mm
		Freckles and red hair	
		Fitzpatrick scale skin type I or II	
	Scottish Intercollegiate Guidelines Network (2003)[28]	11–100 naevi > 2 mm	> 100 naevi > 2 mm
		1–3 atypical naevi	Four or more atypical naevi
		Family history (melanoma in one 1st-degree relative)	Three or more cases of melanoma in 1st-degree relatives
		Fitzpatrick scale skin type I or II	Congenital naevi > 20 cm
		History of high sun exposure	
		History of melanoma	
		Actinic lentigines	
		Light-coloured eyes	
		Light-coloured skin	
U.S.A.	National Cancer Institute (2014)[23]	Multiple naevi	CDKN2A mutation carriers and 1st-degree family members
		Immunosupressed following organ transplant	Patients with multiple atypical naevi
		Family history	History of excessive sun exposure and previous skin cancer

[a]Risk factors from the nine guidelines that differentiated between 'high risk' and 'very high risk' individuals.

clinical assessment of risk; 11 (32%) provided additional recommendations for those at higher risk[15,17,19,20,26,27,30,35,37–39] and nine provided recommendations including screening intervals for both 'high risk' and 'very high risk' populations.[13,14,16,21,23,24,28,31,33] The use of melanoma risk prediction tools was mentioned in two guidelines but their use was not recommended as they required further validation.[14,23] One guideline recommended that a patient's family history be reviewed annually.[23]

There was a general agreement that long-term screening was necessary for individuals at high risk of cutaneous melanoma, particularly where genetic predisposition was identified or suspected because of a strong family history.[13,14,19,21,23,35–37] Twelve guidelines[13–16,19,21,23,31,32,35,36,40] recommended that screening should be based on a prior risk assessment (i.e. an estimate of the risk of developing melanoma demonstrated by the presence of known melanoma risk factors) with intervals defined from 6-monthly to annually,[14,15,21,30,32,35,36] or of 'regular' frequency[13,15,19,23,31,37] or 'lifelong' duration.[16,31,40]

Most guidelines did not discuss genetic testing but for those that did, there was agreement that testing for high-penetrance genes should only be carried out in a research setting or after assessment of family history,[13,21,23,28,35] and where there was provision of adequate support services.[19,30] Six guidelines mentioned the relevance of a family history of pancreatic cancer to genetic testing or the possible need for surveillance for pancreatic cancer in individuals with CDKN2A mutations.[13,16,19,21,23,24] Screening for low-risk genes was currently not recommended.[13,21,23]

Monitoring of naevi

Thirteen guidelines[13–15,19,21,23,24,26,27,29,32,33,35] discussed referral of high-risk individuals to a specialist or dermatologist, or clinical management in a specialist clinic. Recommendations regarding monitoring naevi varied from the provision of patient education regarding recognition[13,24,26] to the need for 6- to 12-monthly dermoscopic monitoring.[18,33,36] Dermoscopy was considered particularly useful for the management of patients with dysplastic naevi,[17,19,21,24,33,38,39,41] facilitating early diagnosis,[41] improving diagnostic accuracy[13,18,19,21,24,26,28–31,37,38,42] and reducing the benign: malignant excision ratio of melanocytic lesions.[13,19,21,37,39] Most guidelines (70%) discussed the need for specialized training for users of dermoscopy, and generally did not refer to clinician subtypes. Total body photography and sequential digital dermoscopy imaging (SDDI)[43] were the two modalities most frequently mentioned. Total body photography was usually discussed within the context of managing high-risk patients with large numbers of dysplastic naevi,[13,19,20,23,30,37,38] and the early detection of lesions.[13,16,19,23,37,38] Short- and long-term monitoring using SDDI was recommended to improve diagnostic accuracy by enhancing the detection of morphological changes over time,

particularly in lesions lacking dermoscopic features of malignancy.[13,18,21,24,27,37–39,44] Some guidelines recommended the use of medical photography to document changes in lesion characteristics.[14,16,17,20,21,24,31,33,37,44] Prophylactic removal of naevi was not recommended in any of the guidelines.

Guideline recommendations for follow-up after a melanoma diagnosis

Review of the follow-up section in the guidelines found fewer risk factors for identifying those at high risk of another second or subsequent primary melanoma, compared with screening guidelines which focused on detection of the first primary cutaneous melanoma (Table 1).

Nineteen (55%) guidelines mentioned previous melanoma as a risk factor for a subsequent primary melanoma; in four (12%) guidelines this was the only risk feature mentioned (Table 1).[38,41,42,45] Targeted monitoring was also recommended for those with dysplastic naevi (32%), or a family history (26%). Ten (29%) guidelines contained recommendations that focused on more than one risk factor.[13,15,19,30,32,35–37,40,46] Supplementary Table S4 shows a summary of the different countries' guidelines regarding follow-up after melanoma diagnosis, applicable to high-risk individuals.

Generally, the guidelines that did identify high-risk criteria for follow-up assessment also provided recommendations regarding follow-up intervals for these groups. Five (15%) guidelines contained a general recommendation that follow-up intervals be based on assessment of risk factors for a subsequent primary melanoma.[32,35,36,40,46] Recommendations for follow-up intervals were usually directed at all patients;[36,37,41,45,47] however, some recommendations were specifically for high-risk individuals and these advised additional 'regular'[13,39] and/or longer 'lifelong' follow-up.[32,36,37] There was not always clear differentiation between the risk of a second primary melanoma and the risk of recurrence.

Guideline recommendations for patient education

Supplementary Table S5 shows a summary of the different countries' guidelines regarding patient education, applicable to high-risk individuals. Recommendations for self-screening or skin self-examination (SSE) were included in 26 (76%) guidelines, and were specifically recommended as part of high-risk management in 13 (38%) guidelines.[13,16,19,20,23,24,26–28,30,31,35,41] Advice on SSE, including the signs and symptoms for suspicious lesions and sun protection strategies, was considered pertinent for the management of high-risk individuals both in the context of screening and follow-up. The definition for SSE is not standardized and we identified three main ways of reporting SSE in the guidelines: (i) a statement with no explanation; (ii) a statement that SSE includes an examination of the skin and palpation of lymph nodes sometimes with a recommended interval; (iii) a detailed explanation of the process[13,14,26] or a reference or website where information could be obtained.[16,19–21,24,26,29,31,36] Recommendations for SSE intervals ranged between monthly,[14,16,23,24,31,33,35,40,47] and 3- to 6-monthly,[13,26] or were not stated.[19–21,27–30,32,36,37,41,42,45,48]

Recommendations for providing education about sun protection was generally well documented; however, explicit recommendations regarding avoidance of artificial sources of UV light was found in only eight guidelines.[14,15,17,20,21,23,31,36]

Guideline audience

Most guidelines did not specifically target 'general practitioners' or dermatologists', but defined a broad audience (53%) or 'clinicians' (27%) as their target audience, reflecting that melanoma patients are often cared for by multidisciplinary teams of healthcare professionals (Table 1). For seven (21%) the audience was not defined.

Quality of evidence supporting the guideline recommendations

A brief description of the evidence base used to develop each of the guidelines is shown in Table 1. All guideline recommendations were based on a review of the literature and a consensus decision, but not all clearly described their methodology. Of the guidelines using a formal classification system (19 of 34), we found variation in both the grades of evidence (3–8 levels) and strength of recommendations (3–6 levels). Three guidelines[20,23,46] provided level of evidence classifications, one[36] a level of evidence and consensus classification, and 15 (43%) provided both level of evidence and grade of recommendation. Five[14,30,31,34,47] (15%) guidelines provided a summary of the level of evidence (but no categories) to support their recommendations.

The level of evidence for specific guideline recommendations aimed at high-risk individuals, graded using the Oxford appraisal tool,[12] is shown in Supplementary Tables S2–S5. There were high levels of evidence supporting assessment of risk factors to identify individuals at high risk of melanoma. There were also high levels of evidence for targeted regular monitoring using dermoscopy and SDDI to increase diagnostic accuracy. There were low levels of evidence for total-body photography. Recommendations for screening intervals and duration of follow-up specifically for high-risk individuals and for SSE were largely consensus-based (level 5 evidence). Sometimes the level of evidence varied depending on the context and terminology used: for example, recommendations regarding dermoscopy ranged from level 1 to 4. If the recommendation referred to the use of dermoscopy to examine dysplastic naevi, then a high level of evidence was applied; but if the recommendation was for 6-monthly screening supported by dermoscopy then a lower level of evidence was applied. In addition, the year in which the guidelines were published meant that the same recommendation could have different levels of evidence. Sometimes similar practices did not have the same level of evidence.

Key recommendations

Table 3 highlights the key recommendations for high-risk individuals that were consistently reported across the different clinical practice guidelines, in relation to risk assessment, management of screening[49–52] and follow-up. Topics covered include use of dermoscopy, prophylactic removal of naevi, duration of screening and follow-up and patient education.

Discussion

There was agreement between different countries' clinical practice guidelines that individuals at high risk of melanoma should be identified and screened, and that individuals should receive follow-up to monitor for new or changing lesions after a melanoma diagnosis. There is high-level evidence about melanoma risk factors, but only limited information in

Table 3 Summary of guideline recommendations for identification and screening of individuals at high risk of melanoma by order of levels of evidence[12]

Item being described	Oxford level of evidence[a]	Summary of guideline recommendations
Risk assessment	1–2	Clinicians should be aware of risk factors and groups known to have substantially increased risk of melanoma
	3–4	Alertness for melanoma-suspicious skin lesions should be increased when individuals have a combination of risk features
	3–4	If familial melanoma is suspected, particularly if an individual has large numbers of naevi, referral to a specialist with an interest in melanoma management is advised
	5	Individuals with melanoma risk factors should be identified by primary healthcare provider and offered surveillance or referred if appropriate to a specialist for surveillance
	5	Assessment of risk should determine the frequency of surveillance for individuals with increased risk due to a combination of risk factors
Screening management	1–2	Training and utilization of dermoscopy is recommended for clinicians routinely examining pigmented skin lesions
	1–2	Consider recording dermoscopic images of lesions over time so changes in the lesion can be identified (sequential digital dermoscopy imaging, SDDI)
	3–4	Consider the use of baseline total-body photography in conjunction with dermoscopy as a tool for the early detection of melanoma in patients who are at high risk for developing primary melanoma
	3–4	Individuals with atypical naevi should be advised to have regular follow-up skin examinations at 6- to 12-month intervals
	3–4	High-risk individuals may benefit from annual surveillance by a dermatologist or trained healthcare provider
	5	Individuals at higher risk should be monitored for life because of risk of malignant change
	5	High-risk individuals may benefit from 6-monthly surveillance with a full-body examination supported by total-body photography and sequential dermoscopy as required
	5	Prophylactic removal of lesions is not recommended in individuals with multiple naevi
	5	Screening for a mutation should not be done until confirmation of family history and genetic counselling
Follow-up after melanoma diagnosis	3–4	Patients with pigmented lesions may benefit from dermoscopic imaging or clinical photography
	5	More regular follow-up intervals could be recommended where patients have a history of previous melanomas, family history of melanoma or the presence of atypical naevi
Patient education	3–4	People with high-risk features should not use solariums
	5	Patients should be educated about self-examination of the skin and lymph nodes, signs and symptoms of melanoma, and photoprotection
	5	Patients at high risk of recurrence or new primary cancers should be instructed in self-examination and be provided with written and photographic information

[a]Oxford levels of evidence: 1–2, high level of evidence; 3–4, lower levels of evidence; 5, consensus-based descisions (lowest level of evidence).

the guidelines for defining 'high' and 'very high' risk groups and these terms are used inconsistently. This should be addressed in future guidelines in order to inform and streamline screening and follow-up management strategies. There is high-level evidence that dermoscopy improves diagnostic accuracy but it is acknowledged that adequate training is important. The use of total-body photography and SDDI[43] have been shown to be effective in detecting malignant changes and new melanomas in high-risk patients[49–51] when compared with melanomas diagnosed in the population by other means, and has led to fewer excisions.[52] However, from these studies it is difficult to estimate which diagnostic technique is more beneficial,[53] and studies using control groups have not been performed. Frequent monitoring has been shown to increase patient compliance for follow-up,[54] and further research on the effectiveness of various imaging modalities is ongoing.[55] The use of specialized 'high-risk clinics' for follow-up management of high-risk individuals is another model of care currently being evaluated in some countries.[56,57]

We found generally low levels of evidence supporting recommendations for screening intervals and follow-up duration for high-risk individuals as reported for other cancers.[58] Levels of evidence are important to assist clinicians in evaluating the strength of the recommendations and may be coupled with opinions from experts to place the evidence in context.[59] Randomized trials of clinical management (nontherapeutic interventions) of melanoma are uncommon; therefore, the best-quality evidence is likely to come from prospective observational studies. We were sometimes unable to rate the strength of evidence for the recommendations, when there were only limited references provided in the guidelines, or when the link between the evidence and the recommendation was unclear, a finding that was also reported in a review of stage-specific surveillance practices.[10]

Due to the increasing cost of long-term follow-up care, consideration should be given to strategies for providing patients and their partners with skills for SSE.[60] There is some uncertainty as to whether it is the patient or clinician who is more likely to detect recurrence or a new primary cutaneous melanoma.[6,61,62] Patient education for SSE may aid in early detection,[61,63] but the potential harms and benefits of SSE require further evaluation.[34] Education regarding SSE is a strategy that is particularly pertinent to high-risk groups. Some guidelines reported that not all patients were able to perform SSE, for example due to advanced age, and thus could require more frequent clinical surveillance. Furthermore, regular physician screening may assist in the management of patient anxiety.[13,30,37,40] Other benefits of screening included opportunities for documentation and review, provision of patient information and support, and identification of patient kindreds.[7,8,36,37,46]

It should be noted that not all guidelines addressed all the topics in this review. For example, some guidelines stated that they focused only on the management of melanoma;[29,36,38,40,45] thus, risk assessment may not have been discussed. Other guidelines focused on prevention and referral and did not include follow-up recommendations.[33,34,44] As we focused on high-risk groups, recommendations for the general population were not necessarily captured in this review.

We suggest some general improvements to the language used in the guidelines, for example: describing risk factors such as 'many naevi' or 'family history' more precisely to provide clarity around recommendations; quantifying the time period for screening intervals rather than defining as 'periodic' or 'regularly'; and differentiating between follow-up recommendations for another primary melanoma vs. the risk of recurrent disease.

While acknowledging the differences in healthcare systems that will affect the referral and management procedures, clinical practice guidelines for melanoma could be further improved by: (i) providing information about how to identify high-risk individuals; (ii) providing specific recommendations for clinical management of individuals defined as high risk; and (iii) discussing strategies for the most efficient way to monitor high-risk individuals for new primary melanomas. Further research applicable to high-risk individuals includes identifying genetic markers, efficacy of novel diagnostic technologies such as teledermatology,[64] benefits and potential harms of SSE and the ideal techniques,[65] and clinical trials to determine optimal follow-up methods[53] and screening intervals. The examination of the benefits and costs of alternative management strategies will also enhance the quality and practical value of recommendations in future guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1. The Oxford 2011 Levels of Evidence.

Table S2. Summary of guidelines regarding assessment of level of risk applicable to high-risk individuals.

Table S3. Summary of guidelines applicable to high-risk individuals regarding screening management.

Table S4. Summary of guidelines applicable to high-risk individuals regarding follow-up after melanoma diagnosis.

Table S5. Summary of guidelines applicable to high-risk individuals regarding patient education.